American Journal of Obstetrics and Gynecology

VOL. 38 NOVEMBER, 1939 No. 5

American Gynecological Society

Sixty-Fourth Annual Meeting, May 22, 23, and 24, 1939

PRESIDENTIAL ADDRESS*

FREDERICK C. HOLDEN, M.D., NEW YORK, N. Y.

FORTY-SEVEN years ago I attended my first meeting of the American Gynecological Society, and recently browsed through the sixty odd volumes of the Transactions. I should like to present a few examples of the great debt which the Society owes to some of its members; to compare briefly its present activities with those of the early days; and last, to discuss certain present-day trends.

The medical historian, J. H. Bass (*Outline of the History of Medicine*, 1889) wrote that gynecology is a specialty "in which American medicine has won, perhaps, its most enduring laurels." Prior to 1850, gynecologic surgery did not exist. In 1876, however, when the most prominent gynecologists from various parts of the United States came together to form the American Gynecological Society, the specialty was already firmly established. In the short space of a quarter of a century, a brilliant and rapid advance had taken place in which the founders of this society played an important role. Well might Fordyce Barker assert in the first presidential address that "in obstetrics and gynecology, the progress in science and its resultant improvement in practice have been greater during the past one hundred years than the whole advance made during the previous ten centuries."

" 'Tis opportune to look back upon old times, and contemplate our forefathers" wrote the learned Sir Thomas Browne. The achievements of Atlee, Sims, Emmet, Peaslee, Goodell and Parvin are an inspiration for all succeeding generations. It is true that many contributions which seemed highly significant a half century ago have proved of

*Read at the Sixty-Fourth Annual Meeting of the American Gynecological Society, White Sulphur Springs, W. Va., May 22 to 24, 1939.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

ephemeral value. For instance, the extirpation of functionally active ovaries, the attention paid to uterine flexures and to stenosis of the cervix—these and many others have very little significance now, but were the subject of mighty battles in their day. It would seem worth while to attempt to evaluate those contributions which record actual advances, contributions which have stood the acid test of time, and which will engage the attention of historians of our specialty for centuries to come.

In the first volume of the transactions, we find Emil Noeggerath's classic contribution "Latent Gonorrhoea, Especially With Regard to Its Influence on Fertility in Women." He set forth startling views which met with great opposition in the ensuing discussion. In closing, the author stated that "after the gentlemen have given five years or more of careful study to this question I shall expect to hear more approval than I have done today." Three years later Neisser isolated the gonococcus.

In 1878, Thomas Addis Emmet contributed a paper on "The Necessity for Early Delivery, as Demonstrated by the Analysis of One Hundred and Sixty-One Cases of Vesico-Vaginal Fistulae." Appearing ten years after his great book on vesicovaginal fistulas, this paper represented his mature views as to the cause of this tragic injury. He pointed out that instrumental delivery was rarely, if ever, the agent in the production of vesicovaginal fistula, but that the direct cause was always delay in delivery. Not "meddlesome midwifery," but delay in the use of forceps was the important factor.

When we remember that the Woman's Hospital in New York was organized and established for the purpose of the cure of vesicovaginal fistula caused by obstetric trauma, we well realize how important a contribution was made by Sims and Emmet to the advance of obstetrics and the great reduction of the incidence of this calamity.

The introduction of anesthesia in 1846 had robbed surgery of its terror. Three great dangers of surgery still remained: shock, hemorrhage, and infection. The year this society was founded was marked by the meeting of the International Medical Congress at Philadelphia. The great Lister himself was present at this meeting and entered into the discussion of the problem of infection. According to Lusk, the views of Lister were received by a curious but unsympathetic audience. The majority of medical men still clung to the idea of spontaneous generation and scoffed at the germ theory of disease.

Not until 1883 was a paper read before the Society applying the ideas of Lister to gynecology. R. Stansbury Sutton read a paper on "Cleanliness in Surgery." The author had a very clear insight of the importance of asepsis implicit in Lister's teaching, while Lusk in the discussion, paid tribute to Lister's great contribution. Albert H. Smith, however, in his presidential address the following year, discussing the etiology of puerperal infection, denied the doctrine of its germ origin. While this debate was going on, three members of the society were proving for the first time in America that the application of asepsis and antisepsis could reduce the dreadfully high mortality in our lying-in institutions. Garrigues, at the Charity Hospital, New York, Lusk, at the

Emergency Hospital and Richardson at the Boston Lying-In, were proving by their results that Lister and Pasteur were right, and those who scoffed at germs were wrong.

In 1887, William M. Polk laid the foundation of conservative gynecological work in this country in a paper entitled "Are the Tubes and Ovaries to Be Sacrificed in All Cases of Salpingitis?" He shares honor with C. Schröeder and A. Martin of Germany for his demonstration of the possibility of restoring function in diseased adherent tubes and ovaries and of the functional value of amputated and opened tubes.

Polk returned to this subject again in 1893 in an article entitled "Operations Upon the Uterine Appendages With a View to Preserving the Functions of Ovulation and Menstruation." The paper created unusual discussion, and warm admiration was expressed for Doctor Polk's courage in taking a position on which he was liable to be attacked from all quarters.

Conservative surgery for pelvic inflammatory disease was further aided by the work of Frank F. Simpson. In 1909, he read a paper entitled "Choice of Time for Operation for Pelvic Inflammation of Tubal Origin." He showed that perhaps the majority of patients with pelvic inflammation have their organs restored practically to normal without operation. He pointed out the danger of operative interference during the acute stage and laid down the rules for the choice of time of operation. Simpson's rules are observed to this day.

John Whitridge Williams presented his work on "Tuberculosis of the Female Generative Organs" partly as a result of which he received the honor of Fellowship in this society when only twenty-six years of age. Three years later he again appeared before the society to present a paper of perhaps even greater importance in the domain of pelvic pathology, "Deciduoma Malignum." This contribution ranks with the important monograph of Marchand which appeared at this time, proving the fetal origin of chorionepithelioma, and was the beginning of an extensive literature on this subject.

In 1902, John T. Thompson, presented a paper on "Ovarian Pregnancy With Report of a Case," in which he demonstrated for the first time a conclusive specimen of ovarian pregnancy.

An epochal paper appeared in 1921 by John A. Sampson on "Perforating Hemorrhagic (Chocolate) Cysts of the Ovary." The following year he read a paper "The Life History of Ovarian Hematomas (Hemorrhagic Cysts) of Endometrial (Müllerian) type." This paper in which Sampson delevoped a new explanation for these hitherto inexplicable growths has been characterized by Robert T. Frank as of great fundamental importance.

Papers dealing with the more basic scientific aspects of our specialty appeared with increasing frequency in the later volumes of the Transactions. Illustrative of the new trend of interest in the physiology of the reproductive tract was the contribution of Robert T. Frank on "The Function of the Ovary" which appeared in 1911.

A paper which stimulated a great deal of discussion and had an enormous influence on obstetrical practice was that of Joseph B. DeLee in 1920, on "The Prophylactic Forceps Operation."

I have recalled to your attention a few of the outstanding contributions of our Fellows which appeared over the space of sixty years. If time permitted, the list could be lengthened considerably. In the operative treatment of fibroids and of prolapse, in the introduction of radiation therapy for cancer and other pathology, in every aspect of gynecology, important work has been done by members of this society.

Of great importance has been the union of gynecology and obstetrics. This was not brought about without a struggle. Theophilus Parvin devoted his presidential address in 1893 to the necessity of the fusion of these two scientific branches. As a supplement to his address, a paper was read by F. Winckel of Munich on "The Necessity of the Union of Obstetrics and Gynecology as Branches of Medical Instruction." Few today would deny their conclusion that progress in obstetrics goes hand-in-hand with progress in gynecology; the one advances the other.

Lusk, fourteen years prior to this time had stated before the Society that he had "nothing but words of praise and honor for those who have contributed so much in the past ten years to perfect the practice of gynecology." He regretted however that "the flattering interest their labors have excited has tended to weaken interest in the sister department of obstetrics. While our young men seem all desirous to make a specialty of the diseases of women, it is hard to obtain a hearing for the statement of the very trite fact that it is midwifery which gives to gynecology nearly all its importance."

In reviewing the history of our specialty, one is bound to compare the program of the first meeting of this Society with that of today. What were some of the presentations in 1876? Forty-six pages about uterine flexures and forty-eight pages about the knee-chest position under the title "Pneumatic Displacement in Dislocation of the Gravid and Non-Gravid Uterus." Extirpation of functionally active normal ovaries in young women as a remedy for a variety of diseases; tumors; obstetric injuries amongst which vesicovaginal fistula was a frequent occurrence, and Noeggerath's paper which has stood the test of time "Latent Gonorrhea With Regard to Its Influence on Fertility in Women."

Spanning the years to today's meeting, what an inspiring vista we have: Increasing accuracy of diagnosis; asepsis and antisepsis with their tremendous influence; the rapid improvement in surgical technique; the progress in anesthesia and in preoperative and postoperative care; the microscope with its influence on pathology and bacteriology; radiotherapy; and always increasingly in evidence, the continuous advancement of medicine into the realm of pure science particularly in endocrinology. There has likewise been commendable advance in the teaching and training of our doctors. On the other hand there is intensive training of a small group of experts. Of equal importance is the better training of the general practitioners, particularly in the field of obstetrics, by planned postgraduate lectures, and hospital guidance, as carried out by the policy of an open courtesy visiting staff in some of the leading obstetrical hospitals.

As we glance over today's program, clinical medicine is in the background while scientific investigation, especially in that fascinating field of endocrinology, comes more and more to the foreground.

In our Society today, along this span between the old and the new, we have a group of eminent clinicians who would be unable to discuss many of the papers presented today, because of lack of knowledge. We have had difficulty in getting men to discuss some of today's papers, because the only ones who can discuss these papers are those who wrote them.

We see therefore the amazing progress from empirical medicine to the rapid and increasing advancement of the science of our specialty. Although we feel justifiable pride in this scientific progress, let us not lose sight of the fact that the art of medicine remains of equal importance. The art of medicine must continue to be taught, practiced, and its growth and development encouraged. Patients are human beings and not guinea pigs, and the ills of the human body cannot and must not be completely disassociated from the mental, emotional and psychic content of the individual we are treating.

Our world of today is becoming rapidly more complex. Great forces are at work, many of them capable of destroying all of our constructive efforts. Social programs of national scope affecting the health and well-being of our people are in the process of formulation.

We as a group, the individual members of which are recognized leaders in our respective communities, must assume our full responsibilities and accept our duties of leadership towards the direction that we think right. This means not only the teaching and practice of our specialty, it means not only scientific research, but today it also means taking an active part in formulating that part of the national health program which will be the deciding factor as to what kind of medical care will be given to our nation, and how it is to be administered. We can no longer retire to our clinics and laboratories, but must take our proper places in all broad programs of social welfare which affect the health of our people.

The early great physicians of this country because of their learning and leadership were looked to for advice in all the problems of the body politic. In order to carry through those principles which we think are essential for the preservation of freedom and scientific thinking, and the maintenance of the highest type of medical care, we must include in our program an awareness and participation in every angle of medical care and of its administration.

Our Society might properly be the consultation board for any legislation affecting particularly maternal welfare and any other public health program coming within the scope of either branch of our specialty. I strongly urge this Society to recognize the importance of this legitimate extension of its activities and responsibilities. Our expert knowledge and policies should be in advance and guide all such legislation.

I have the greatest confidence that the American Gynecological Society will continue as the wise and great leader in all the scientific, medical and social aspects of our specialty.

59 East 54th Street

THE RELATIONSHIP OF THE ESTROGENS AND OTHER PLACENTAL HORMONES TO SODIUM AND POTASSIUM BALANCE AT THE END OF PREGNANCY AND IN THE PUERPERIUM*

HOWARD C. TAYLOR, JR., M.D., ROBERT C. WARNER, M.S., AND CATHERINE A. WELSH, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, New York University College of Medicine and the Obstetrical and Gynecological Service of the Third [New York University] Surgical Division Bellevue Hospital)

TWO distinct general conceptions of the nature and origin of the toxemias of pregnancy have guided recent research in two apparently quite divergent channels. In one direction are the endocrines, a very promising field, for it seems hardly possible that the substances which determine to such an extent the characteristic physiologic changes of pregnancy should not be in some sense responsible for a disease which occurs only in pregnancy. On the other hand are the physical and chemical phenomena of water and electrolyte exchange, which for the moment seem more closely related to the classical symptoms and signs of pre-eclamptic toxemia. Recent experiments showing that the estrogens and progesterone may cause the retention of sodium and of water suggest a line of investigation by which the hormonal and the physicochemical conceptions of toxemia may perhaps be reconciled.

The precise intention of this study has been to determine whether in pregnancy changes in the concentration of the estrogens and other placental hormones have any effect on the retention and excretion of sodium and potassium. The general method of investigation has been the measurement of the balance of sodium and potassium intake and output during alterations in the hormone content of the blood and the urine. The changes in hormone concentration made use of have been those occurring at parturition, after intrauterine death of the fetus and those following the intramuscular injection of estrogenic substances.

THEORETICAL CONSIDERATIONS

Before proceeding to the report of the present study, it is necessary to mention certain previous clinical observations and experiments which appear to make important an investigation that is concerned with sodium and potassium, with the placental hormones and with the relationship between hormones and electrolytes.

1. Sodium. There is good reason to believe that sodium is one factor in the production of those symptoms or signs of toxemia which are dependent on the retention of fluid. This is the rationale for the low salt diet which forms such an important part of the currently popular dehydration therapy for pre-eclampsia. Two

*Read at the Sixty-Fourth Annual Meeting of the American Gynecological Society, White Sulphur Springs, W. Va., May 22 to 24, 1939.

This study was carried out with the aid of a grant from the Commonwealth Fund.

years ago before this society De Snoo[34] presented figures to show that a low salt diet diminished the incidence of eclampsia, and more recently Strauss[37-39] has described the exacerbation of symptoms which follows the administration of sodium salts to toxemic patients with low plasma proteins.

2. Potassium has never been so clearly associated with pre-eclampsia. In high serum concentration this ion is known to have certain toxic effects[31] and may under special experimental conditions be responsible for elevations in blood pressure.[5, 16, 23, 26]

The principal reason for the inclusion of potassium in this study, however, was the contrast which it was hoped its behavior might afford to that of sodium, for the normal physiology of these two ions in the body is strikingly different. Potassium is the predominant basic ion within the cells, but is present in very small quantities in the blood plasma, whereas sodium is almost entirely restricted to the extracellular fluids. Furthermore certain endocrines, particularly the hormone of the adrenal cortex, produce opposite effects on these two ions, namely a retention of sodium and an excretion of potassium. A correlated study of the excretion of these two elements will help to distinguish between the intra- and extracellular sources of excreted water and may perhaps give some insight into adrenal function.

3. The placental hormones as isolated substances have for several years been a subject of research for a cause of toxemia. Various abnormalities such as an increase in prolan concentration, a fall in estrogen[32, 41] and pregnandiol excretion and an alteration in the estronestriol ratios,[33] have been observed.

4. That a hormone was capable of causing a retention of sodium and of water was first conclusively demonstrated for a substance obtainable from the adrenal cortex,[13, 14] and now known as corticosterone. Between corticosterone and certain of the sex hormones there exists a close similarity of chemical structure. Suspecting that physiologic similarities might exist as well, Thorn and Engel[42] have injected estrone and estriol into dogs and have observed a cortinlike effect in the decreased excretion of sodium.

The sodium retaining effect of the estrogens and progesterones has already been given a clinical application in an explanation of the so-called menstrual edema (Thorn, Nelson and Thorn[45]). If the hormones of the menstrual cycle are capable of causing retention of sodium and of fluids, there is considerable reason at the outset to expect a more marked retention of these substances in pregnancy, when the hormones are effective in much greater concentration and over a much longer period of time.

A similar sodium retaining effect has been reported by Klodt[18] to follow the injection into rats of the gonadotropic hormone of the anterior lobe of the pituitary gland. Some delay in the onset of the decreased sodium excretion suggests the possibility that this effect might have been produced by the estrogens or progesterone released by the rat's own ovary as a result of stimulation by the injected anterior pituitary hormone. Until this is proved, however, the gonadotropic placental hormone must also be given consideration as a cause of sodium retention.

THE ORGANIZATION OF THE INVESTIGATION

In setting out to study this field, the period just before and after parturition seemed to us of most value. The separation of the placenta is followed by what must be the most abrupt endocrine changes that ever occur, so that the early puerperium is almost ideally adapted to the study of hormone-electrolyte relationships.

The sodium and potassium balances of six patients accordingly have been determined during the last few weeks ante partum, during labor, and the first ten post-partum days and correlated with the changes taking place in the concentrations of the various placental hormones during the same period. Three of these patients were untreated normal pregnant women. Two were toxemic patients, one developing the com-

plication of fetal death during the period of observation. The last case was again a normal pregnancy, but this patient received large doses of estrogens on the sixteenth and fifteenth days before delivery and again during her first five post-partum days.

The patients were admitted from the ante-partum clinic and were hospitalized on the obstetric ward of the Bellevue Hospital during the period of study. Partial isolation was obtained by the use of an alcove on the ward. The diet was prepared in a small kitchen adjacent to the ward, used for no other purpose, and cooking and serving of the meals was in the hands of a nurse-dietitian whose sole duty was the care of these patients.

The Intake.—The patient was kept on a normal mixed diet, similar to that which she might have selected for herself at home. Three sets of meals differing somewhat from each other in actual make-up, but to a very slight extent in sodium and potassium content, were used. Diet "A" was made up of 228 gm. of carbohydrate, 75 gm. of protein, and 125 gm. of fat. The estimated content of potassium was 3.31 gm., of sodium 2.37 gm. Diet "B" contained 211 gm. of carbohydrate, 79 gm. of protein, and 125 gm. of fat. The estimated content of potassium was 3.32 gm., of sodium 2.36 gm. Finally a soft diet was planned for use on the day of labor and on the first post-partum day. The "labor diet" contained 168 gm. of carbohydrate, 80 gm. of protein, and 119 gm. of fat, the estimated potassium and sodium content being 3.33 gm. and 2.29 gm., respectively. The intake of sodium was intentionally placed at a rather low level so that no danger would be incurred by patients with edema. At the beginning of each three-day period food was purchased to make four complete diets of either the A or B type. This diet was fed for three days and a fourth complete day's feeding made up and cooked in an identical manner for analysis of sodium and potassium in the laboratory. To afford the patients some variety, a change was then made to the other diet, which was fed for another three-day period and a fourth set of three duplicate meals again made up for analysis. This alternation of these diets with an analysis every third day was continued throughout the tests. The figures for sodium and potassium on the intake side of the balance were thus based on actual analysis of duplicate food sample, and never upon estimated figures.

When labor began the patient was placed on a soft diet. If any food was refused during this period, the residue was preserved and analyzed and the amounts of sodium and potassium found were subtracted from the figures for the full day as obtained by analysis of a duplicate day's diet. In order to keep the intake as nearly constant as possible, known amounts of sodium and potassium chloride were administered in capsules to make up for the estimated deficiency due to food refused. These additions were of course accounted for in calculating the day's intake. The labors of all except one of the cases studied were fairly short and uncomplicated so that little difficulty was encountered in the feeding problem. Each patient had returned to one of the antepartum diets by the second post-partum day.

A liter of water was allowed daily in addition to that of fluid food material. The total daily fluid intake during the time of the A and B diets was 2,410 c.c.; during the two days of soft diet, 2,780 c.c.

Before making any measurements of either electrolytes or hormones, the patients were fed with one of the standard diets for several days, in most cases for a week. This served as a period of training of the patient in her routine and of stabilizing her intake and output. The graphs to be presented in each case begin only after this preliminary period had been completed.

COLLECTION OF EXCRETA AND OTHER SOURCES OF LOSS

The estimation of sodium and potassium loss from all possible sources during pregnancy, labor, and the puerperium is a complicated procedure and undoubtedly subject to several errors.

Urine was collected in especially cleaned containers, which were sodium and potassium free. These specimens during the ante-partum period were voided, but

immediately after labor a retention catheter was inserted and the urine collected by this means during the first week of the puerperium so that contamination with the lochia could be avoided.

Feces were obtained by spontaneous evacuation or following the use of distilled water enemas.

Vomiting occurred in two cases during labor. The sodium and potassium figures on the vomitus were determined and subtracted from the day's intake.

Milk.—Only two patients were allowed to nurse their babies. In each instance the babies were weighed before and after nursing, and samples for analysis were obtained by pumping the breast at each feeding. The total daily loss was of course the amount found in the sample added to the estimated amounts obtained by the baby.

The *lochia* afforded special difficulties. Vulval pads made of disintegrating material were packed in a large glass jar which was sterilized and weighed. After use the pads were returned to the jar which was again weighed, the increase being regarded as the weight of the lochia.

Amniotic Fluid.—When the cervix had attained about three fingers' dilatation during labor the patient was placed on a bed pan and the membranes ruptured. A sufficient quantity of relatively uncontaminated amniotic fluid was then obtained for analysis. The total volume of amniotic fluid was taken as the amount lost at this time, plus the increase in weight of vulval pads worn thereafter until delivery, plus the fluid lost immediately after delivery. The sodium and potassium of the amniotic fluid was not, however, added to the balance figures, because this was regarded as already outside of the maternal system at the time of its loss, and there was little reason to suppose its volume had greatly changed during the antepartum period of study.

Blood lost after the delivery of the baby was collected, analyzed and applied to the negative side of the balance. It accounted for a slight increase in sodium loss notable in one or two cases on the day of labor. The blood taken for specimens during the course of the study was also considered in the balance, since with the large specimens needed for hormone analysis the electrolyte loss by this means is not negligible.

Loss by perspiration has not been taken into consideration. Since we were interested particularly in contrasting trends of electrolyte excretion before and after labor and the factor of perspiration was presumably more or less constant, the omission of the study of sodium and potassium loss by this channel did not seem to introduce any serious error. Freyberg and Grant[9] have reported a daily loss by perspiration of 0.133 to 0.179 gm. of potassium and 0.071 to 0.209 gm. of sodium. A daily loss of 0.15 gm. of potassium and 0.10 gm. of sodium may perhaps be assumed.

TECHNICAL DETAILS OF CHEMICAL DETERMINATIONS

The work required determinations of sodium and potassium on a variety of materials and the assay of estrogens, gonadotropic hormones and pregnandiol.

Determinations of Sodium and Potassium.—a. Sodium was determined by precipitating it as sodium zinc uranyl acetate according to the method of Ball and Sadusk.[2] The precipitations were allowed to stand over night, after which they were vigorously stirred in a water bath maintained at 14° to 16° C. The amount of precipitate was estimated by the colorimetric method of Salit.[29] The colors obtained by this procedure, after allowing forty-five minutes for color development, were read on an Evelyn photoelectric colorimeter using a 520 μ filter. Under these conditions the light absorption conformed to Beer's Law over a concentration range corresponding to 25 to 80 per cent absorption. This was not found to be true using other filters. Standard sodium solutions were run with each series of determinations.

b. Potassium was determined by the method of Truszkowski and Zwemer.[46] The final colors were read on the Evelyn photoelectric colorimeter. Since this instrument

requires a less intense final color than that used in the original method an extra dilution of the alkaline nitrite solution was made and the color was developed in the colorimeter test tube. Using this dilute solution, it was found necessary to allow one and one-half hours for full color development. The colors were read on a 520 μ filter. At this wave length they conformed to Beer's Law between 45 and 70 per cent absorption, and dilutions were always made to give colors falling within this range. Standard potassium solutions were run with each series of determinations. In analyzing urine and food the actual amount of potassium taken for precipitation was increased about ten fold over that used for plasma.

Preparation of Materials.—a. Plasma samples were prepared for analysis by precipitating the proteins with solid mercuric chloride and the phosphate with solid calcium hydroxide (Butler and Tuthill,[4] Holmes and Kirk[15]). For potassium analysis the method of Truszkowski and Zwemer[46] was used. Amniotic fluid was treated by the same procedure.

b. Food samples: The liquid and solid portions of a total daily diet, made up and cooked in a manner identical with the diet administered to the patient, were collected separately and weighed. Any meat in the diet was put through a meat chopper and added to the remainder of the solid food which was then put through the meat chopper twice more. The liquid food was next added to the ground solid food and the combined samples were vigorously shaken in a large jar to obtain a uniform suspension. A sample of about 100 gm. was immediately weighed into a Kjeldahl flask and then digested with sulfuric and perchloric acids. A small aliquot of this digest was evaporated to dryness in a crucible with care to keep the solution well below the boiling point. The residue was taken up in dilute nitric acid, and solid calcium hydroxide was added to remove the phosphate. Sodium was then determined on this solution.

Since it is necessary to remove the ammonium ion from the sample for potassium analysis, an aliquot of the alkaline calcium hydroxide solution was carefully evaporated to dryness. The residue was taken up in dilute nitric acid and potassium was determined on this solution. Tests showed that the solution at this point was free from both ammonium and chloride ions.

c. Urine samples were digested with sulfuric and perchloric acids in small crucibles with final evaporation to dryness. Further treatment was carried out as on the food samples.

d. Specimens of vomitus were analyzed as food, the entire amount being as a rule digested.

e. Feces were made up into a uniform paste with distilled water and were then sampled and digested by the methods outlined for the food.

f. The lochial specimens were brought to the laboratory on pads and were then disintegrated in distilled water. A measured amount of water was used and the mixture stirred until the pads were broken up, and the lochial material had dissolved. Sufficient fluid for analysis was drained off and treated according to the methods for blood plasma.

g. Breast milk was prepared for sodium analysis by treatment with solid calcium hydroxide and trichloracetic acid to remove the phosphates and proteins, respectively. For potassium analysis the proteins and chlorides were precipitated in the manner noted for the plasma determinations.

THE ACCURACY OF SODIUM AND POTASSIUM DETERMINATIONS

The errors in the actual chemical procedures on food and excreta are relatively small, for it was found that duplicate analyses agreed to within ± 1 per cent and ± 2 per cent of the mean for sodium and potassium, respectively. Greater errors, however, were certainly involved in the collection and preparation of material for analysis.

1. The error in plasma determinations on amounts as small as those used is also larger. A special difficulty is encountered in the measurement of plasma potassium, where as a result of the passage of potassium into the plasma from hemolyzed cells the determination is subject to a possible positive error of perhaps 10 per cent.

2. Lochial figures are unquestionably less accurate than those for food and urine because of the method of collection and extraction from the pads. However,

the amounts of sodium and potassium contributed to the balance by the lochia are so small as to make any error incurred in the balance almost negligible.

3. The determinations on food are subject to two errors in addition to those inherent in the technical method. There is one error involved in the weighing, preparing and cooking the supposedly identical diets and a second in the sampling for analysis. The latter error was reduced by using large samples (100 gm.) of the mixed food. The former can be kept down only by painstaking attention to detail by the person in charge of the preparing of the food.

To test the accuracy of the figures arrived at for the food, the dietitian was instructed to make independently and send separately to the laboratory for analysis four complete twenty-four-hour feedings. Two samples of each of these were taken for analysis and each sample run in duplicate. The percentage deviation from the mean of the two samples was 1.2 per cent for sodium and 3.9 per cent for potassium. The percentage deviation of the mean from the average for the four separate diets, in general a measure of all errors involved, was 3.7 per cent for sodium and 4.8 per cent for potassium.

TECHNIQUE OF HORMONE DETERMINATION

Hormone assays were carried out with few changes from the technique described in a previous paper (Taylor and Scadron[41]). A few alterations in method alone need be noted.

1. Estrogens: Owing to the small quantities of estrogens present in post-partum specimens of urine, these had to be extracted after hydrolysis to obtain sufficiently concentrated material for assay. In order to make the ante-partum specimens comparable these also were extracted. The technique used was that of Kurzrok and Ratner[22] in which ethyl acetate is used as a solvent.

For assay of the urinary estrogen, the number of rats used for each level was increased to eight except for specimens from the latter post-partum days when the estrogen content of the urine is too low to permit the use of so many. One rat unit was said to be present when the vaginal spreads of 6 of the 8 animals showed complete cornification. In our experience one such rat unit is equivalent to about 3.5 γ of estrone.

For the serum four rats were injected with the estrogen content of 4 c.c. of blood serum divided into four doses. A full rat unit of the type described is rarely present in 4 c.c. of serum so that degrees of estrus dependent on the character of the cell mixture of the vaginal spread were noted on a scale of 0 to 4 as described by Frank.[8] On the basis of experience obtained from the injection of 800 rats equivalents have been worked out so that partial reactions might with some justification be expressed as given fractions of a rat unit. The method is crude and certainly yields only approximate values. The blood estrogen figures obtained from specimens before and after labor are, however, comparable at least on a qualitative basis. The low values for serum estrogen noted may be explained partly by this method of calculation, partly by the fact that sera were not hydrolyzed so that only the free hormone was being measured.

2. Prolan determinations on ante-partum specimens were made exactly as in the previous report. All sera were extracted to remove contaminating estrogens. Post-partum specimens of urine after the second post-partum day, owing to the large volumes which had to be used to demonstrate one unit, were precipitated with 10 per cent tannic acid according to the method of Levin and Tyndale[24] instead of with alcohol.

3. Pregnandiol in the urine was determined by the method of Venning.[47, 48] Two acetone precipitations were routinely performed, but melting point determinations were begun only after the first four cases had been completed.

THE CONSTRUCTION OF THE CHARTS

The relationship of the hormones to the balance of sodium and potassium is shown in Charts 1 to 6. In the sodium and potassium chart the net daily gain or loss of these elements, with all measured sources of intake and excretion considered,

is plotted in relation to the days before and after delivery. The values for pregnandiol are also plotted directly on the ordinates as milligrams.

The estrogens and the prolan figures are plotted in rat units on a logarithmic scale which emphasizes the differences in the lower values and minimizes those between the higher ones. This was a necessary method in order to make charts of a practical size and shape, but it was also consistent with the ratios of the dose levels used in the assay of the unknown extract.

Furthermore it is not improbable that from a physiologic standpoint the difference between 50 and 100 units is more comparable with the difference between 1,000 and 2,000 than between 1,000 and 1,050.

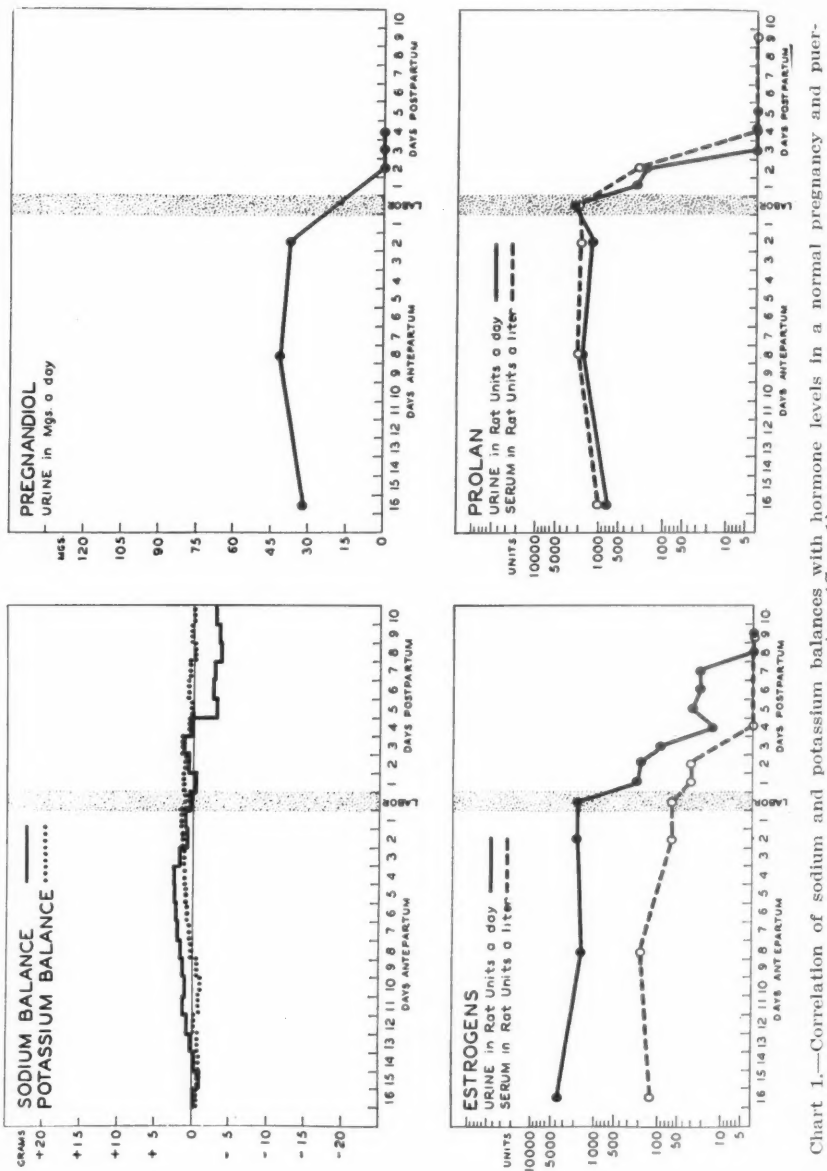

Chart 1.—Correlation of sodium and potassium balances with hormone levels in a normal pregnancy and puerperium (Case 1).

RELATION OF SODIUM AND POTASSIUM BALANCE TO HORMONE CONCENTRATIONS IN THREE UNTREATED NORMAL PATIENTS

Three women admitted toward the end of a normal gestation were studied during the last weeks of their pregnancy, during labor, and during their first ten post-partum days.

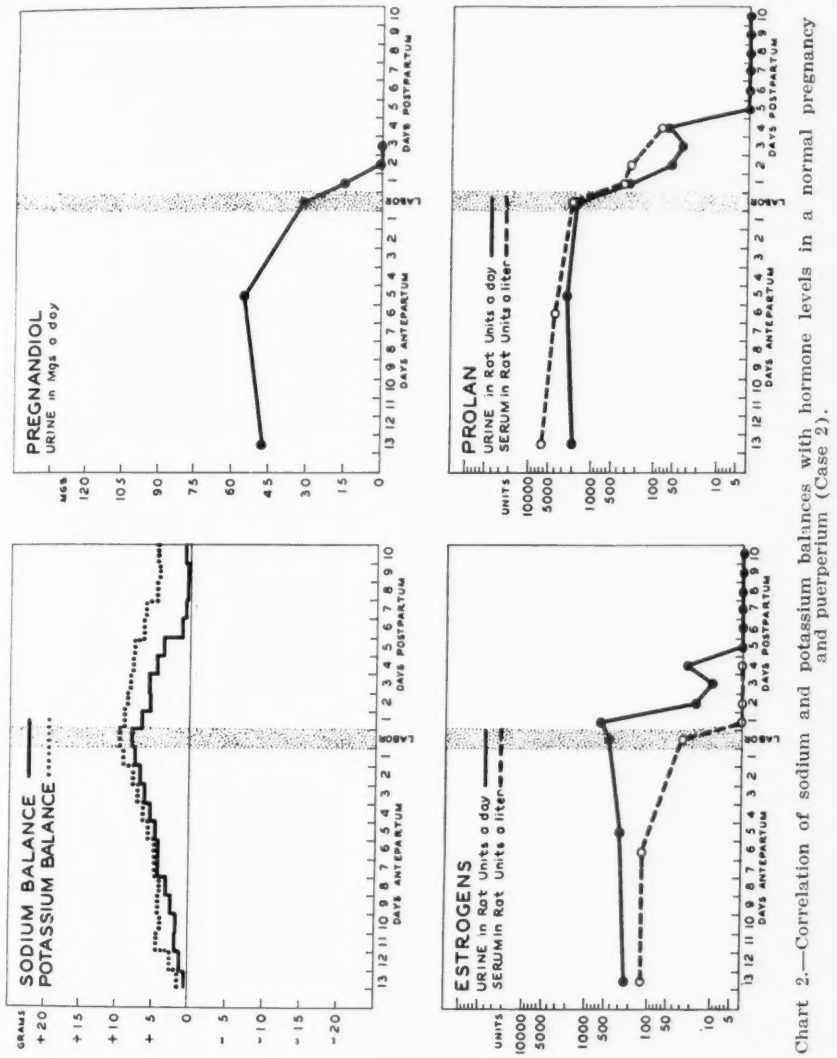

Chart 2.—Correlation of sodium and potassium balances with hormone levels in a normal pregnancy and puerperium (Case 2).

CASE 1.—M. M. (History No. 108879), admitted on April 10, 1938. This patient, a 17-year-old primigravida, had been followed throughout a quite normal pregnancy in the ante-partum clinic. Her last menstrual period was on July 17, 1937. She was normally delivered on May 5, 1938 of a 7 pound, 14 ounce male after a labor of sixteen hours. The blood loss at delivery was 513 c.c. She did not nurse her baby. The post-partum course was complicated by low grade fever, proteinuria and pyuria as a result of cystitis perhaps due to the retention catheter.

CASE 2.—M. G. (History No. 85113), admitted on Sept. 5, 1938. This was a 36-year-old para ii, who had had her last menstrual period on Nov. 12, 1937, and a subsequently normal pregnancy as observed in the ante-partum clinic. Her course in the hospital was also normal, and on September 27 after a labor of eleven and one-half hours she was delivered of an 8 pound, 11 ounce male child. The blood loss at delivery was 200 c.c. The patient attempted to nurse her baby, but her supply of milk was scant. Her post-partum course was entirely normal.

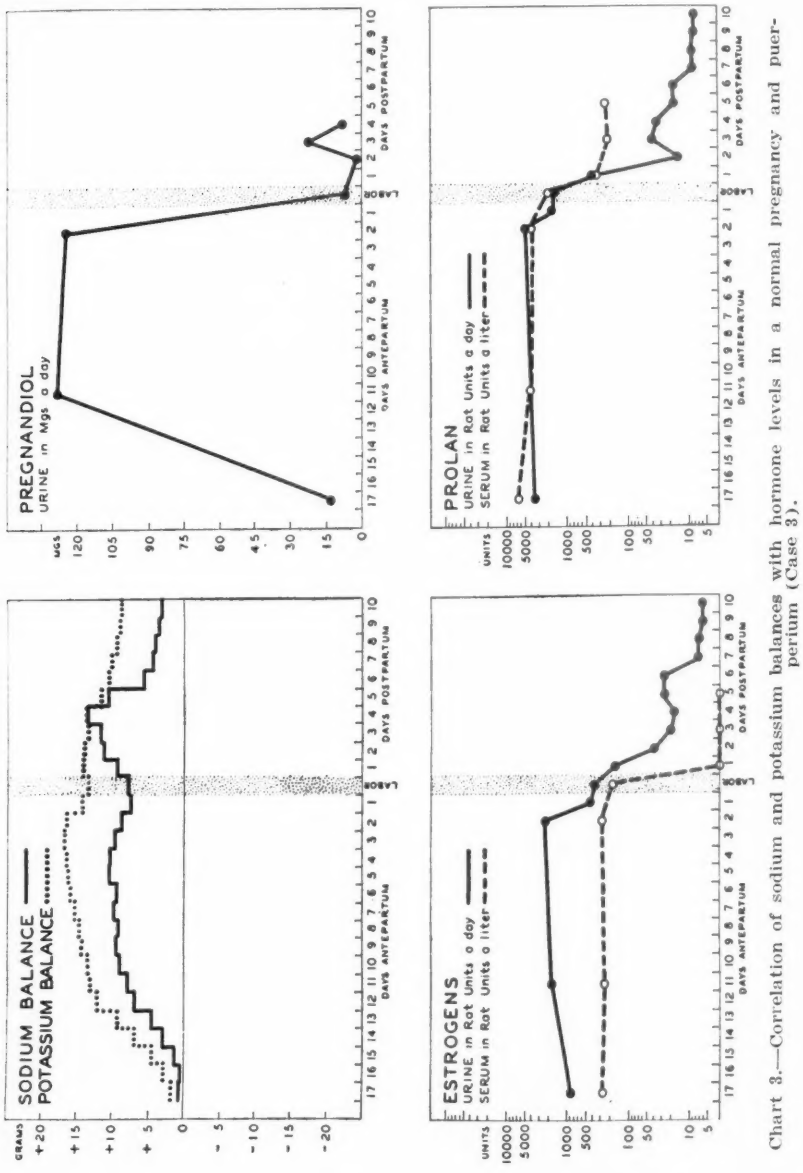

Chart 3.—Correlation of sodium and potassium balances with hormone levels in a normal pregnancy and puerperium (Case 3).

CASE 3.—M. P. (History No. 122209), admitted Oct. 11, 1938. This patient was a 17-year-old primigravida who gave a history of a last menstrual period on Jan. 25, 1938 and a normal pregnancy thereafter. This patient had been living under restricted economic conditions before admission, and there was considerable question

of the adequacy of her customary diet. Her ante-partum course in the hospital was normal, but her labor which was prolonged to fifty hours, on account of slight disproportion, was terminated by midforceps. The blood loss amounted to 375 c.c. The baby, an 8 pound 10 ounce female, was nursed. The post-partum course was nonmorbid and otherwise normal.

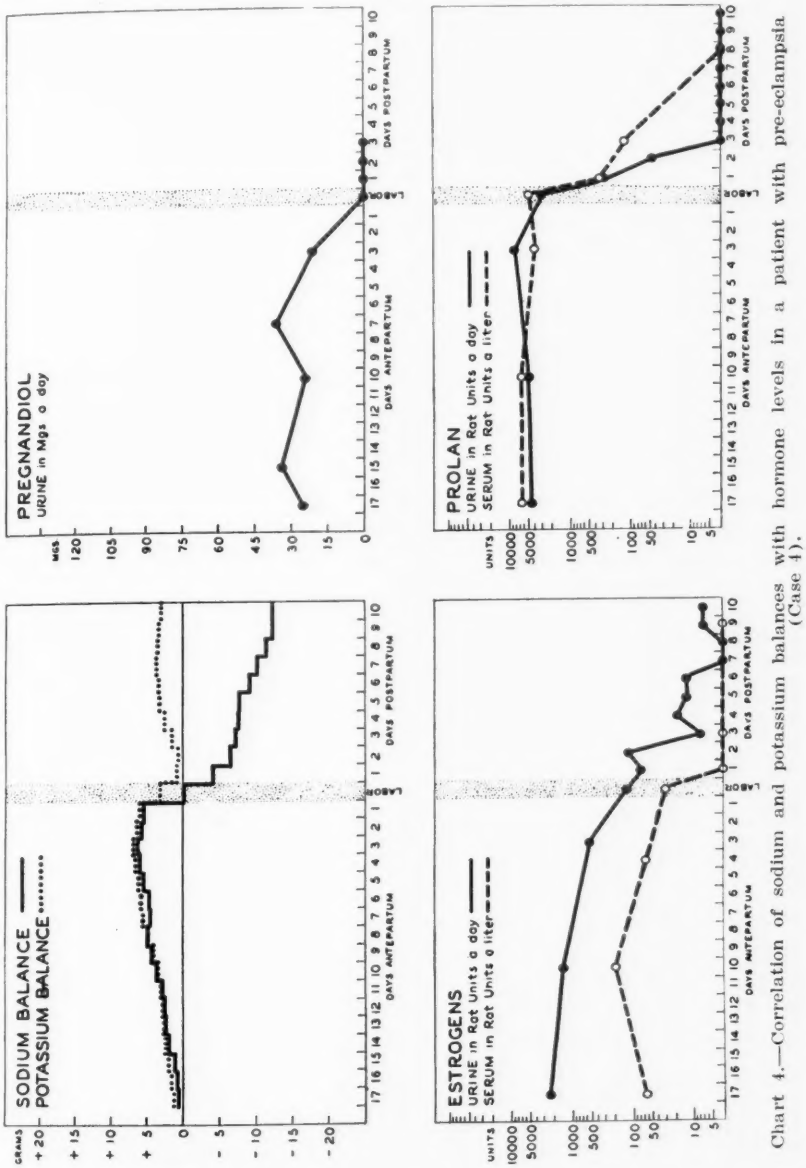

Chart 4.—Correlation of sodium and potassium balances with hormone levels in a patient with pre-eclampsia (Case 4).

Certain features were common to the three normal cases (Charts 1 to 3). The estrogens before labor gave values in the urine varying from 200 to 3000 rat units per liter or in a range similar to those previously reported (Taylor and Scadron[41]). The values dropped very abruptly after labor and by the third day the amounts obtained were reduced practically to those of nonpregnant women.

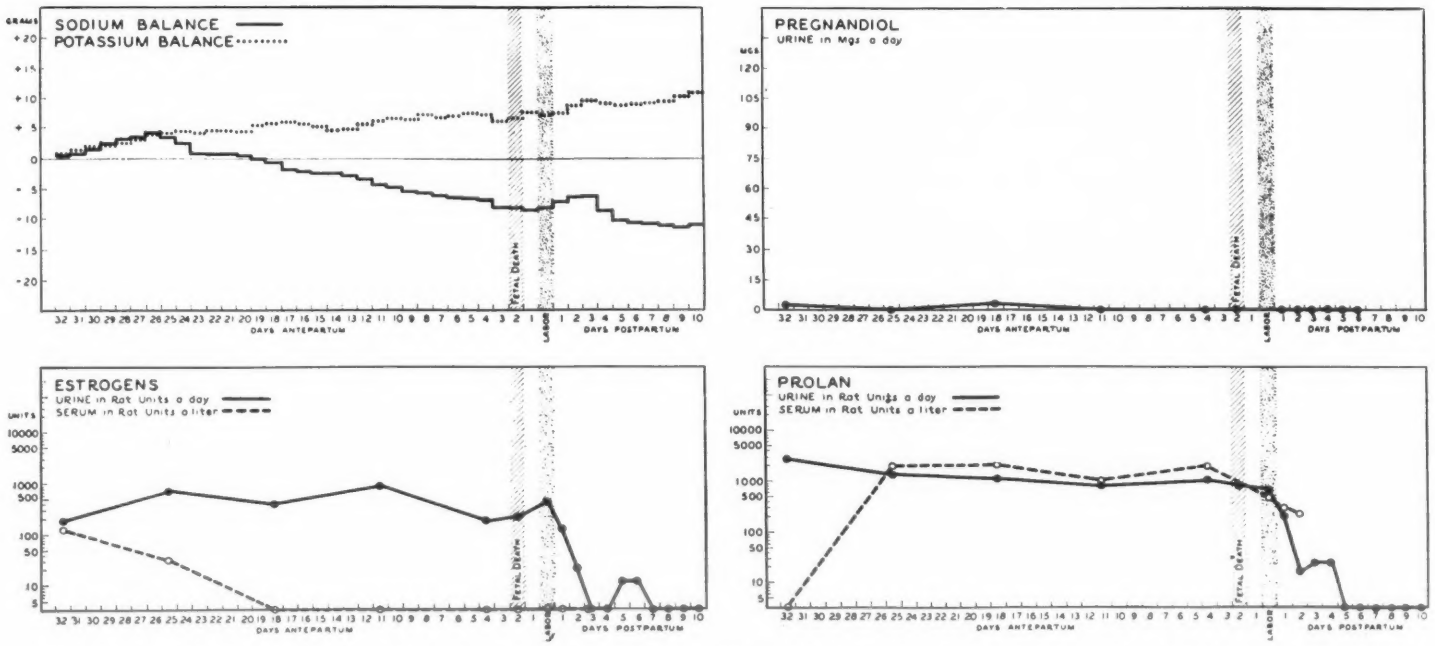

Chart 5.—Correlation of sodium and potassium balances with hormone levels in a patient with pre-eclampsia and fetal death (Case 5).

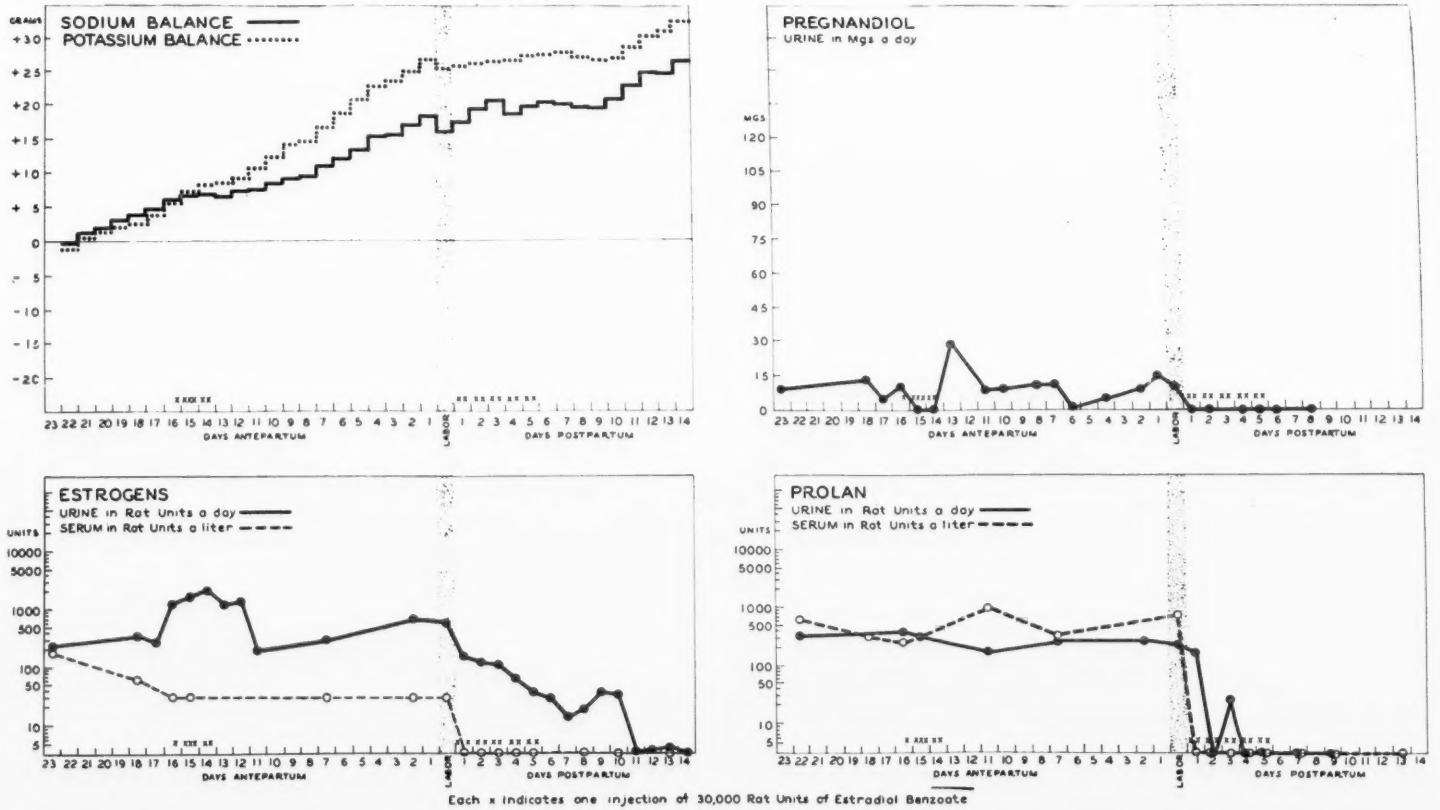

Chart 6.—Correlation of sodium and potassium balances with hormone levels in a normal patient receiving estradiol benzoate (Case 6).

Pregnandiol values in the ante-partum period also varied in a wide range from 13 to 120 mg. in a twenty-four-hour urine specimen. The highest values were possibly errors, since melting point determinations were not made on these particular specimens. Pregnandiol disappeared even more quickly than the estrogens and was as a rule absent by the third post-partum day.

Prolan values before delivery ranged from 750 to 4,700 rat units a day in the urine and from 2,000 to 6,667 rat units per day in the serum. This substance also fell rapidly after labor, but 25 units could often be found until the third or fourth day and the effects of traces were evident in the ovaries of the test animals injected even with extracts of eighth- or ninth-day urines.

The sodium balance was slightly, but almost consistently, positive in all three cases up until the time of labor. This is in agreement with previous studies.[6, 10, 17] The trend was somewhat irregular during the first few post-partum days with at first perhaps a little retention. On the fifth or sixth day, however, there was in each case a pronounced negative balance due chiefly as can be seen from Table I, II and III to an increased excretion of sodium in the urine. In two cases the gains in the ante-partum period were relatively slight, but in one the total amounted to 13.5 gm. in twenty days. This was the patient who, it was believed, had been living on a generally deficient diet before she was admitted to the hospital. The potassium tended to be retained in a little larger amounts before labor and to be lost more slowly afterwards than the sodium.

Comment.—In the ante-partum period no correlation was possible between the actual amounts of hormone present in the urine or blood and the rate of sodium and potassium retention.

The striking feature common to all cases was the post-partum increase in sodium loss, chiefly in the form of sodium excretion in the urine, which usually began on the fifth post-partum day or shortly after the estrogens and progesterone had fallen to levels for nonpregnant women (Tables I to III). A slight retention during the first two or three post-partum days was also perhaps a significant finding.

RELATION OF SODIUM AND POTASSIUM BALANCE TO HORMONE CONCENTRATION IN A CASE OF PRE-ECLAMPTIC TOXEMIA

One case of relatively severe pre-eclamptic toxemia ending in the delivery of a normal child was studied in a similar manner.

CASE 4.—L. D. (History No. 112475), admitted on June 4, 1938. This patient was a twenty-year-old primigravida, giving Sept. 1, 1937 as the date of her last menstrual period. She had been followed in the ante-partum clinic from her second month. Her course had been quite normal until near the end of her eighth month, when she suddenly developed hypertension, moderate edema of the lower extremities, and proteinuria. During her month's stay in the hospital before labor her condition remained essentially unchanged, large quantities of protein being constantly present in the urine and the blood pressure varying from 190/120 to 138/100 (see Table IV). On July 6, 1938 after ten hours of labor she was spontaneously delivered of a 5 pound, 6 ounce female child with a blood loss of 175 c.c. She did not nurse the baby. Her post-partum course was uncomplicated. The signs of hypertension and proteinuria tended to lessen and on her discharge on the tenth day the blood pressure was 136/90, and the urine contained only 1.2 gm. of protein.

The hormone curves for this patient (Chart 4) were in general similar to those for the normal cases. Relatively low estrogens and pregnandiol and high prolan concentrations were present, a finding said to be a characteristic of the disease from which the patient was suffering.

Sodium was retained before delivery in this case as in the normal patients. The post-partum curve corresponded in form to that of the normal cases, but showed a greater loss of sodium. The great excretion of salt in the post-partum period

TABLE I. CLINICAL DATA WITH SODIUM AND POTASSIUM VALUES IN PATIENT M. M. (CASE 1)

	CLINICAL				SODIUM				POTASSIUM			
DAYS	BLOOD PRESSURE	WEIGHT IN POUNDS	PROTEINURIA GM./LITER	URINE VOLUME C.C./DAY	PLASMA MG. %	URINE GM./DAY	FECES GM./DAY	LOCHIA GM./DAY	PLASMA MG. %	URINE GM./DAY	FECES GM./DAY	LOCHIA GM./DAY
16	94/64	131¼	Trace	2300	298	2.72	0.001		19.0	3.54	0.146	
15	120/60	131¼	Trace	2210		3.42	0.001			3.15	0.146	
14		131¼	Trace	2170		2.00	0.001			3.31	0.146	
13	108/54	131½	Trace	2060		2.25	0.0006			3.31	0.233	
12	92/62	132¾	Trace	1500		1.68	0.0006			2.87	0.233	
11	112/64	132¾	Trace	1680		1.95	0.0006			3.90	0.233	
10	120/64	132¾	Trace	2340		2.69	0.063			3.44	0.276	
9		132½	Trace	2150		2.10	0.063			2.72	0.276	
8		132	Trace	1990		1.99	0.063			2.78	0.276	
7		132¼	Trace	1910		2.23	0.063			2.70	0.276	
6		132¼	Trace	1860		2.49	0.063			2.88	0.276	
5		132¼	Trace	2020		2.48	0.063			3.23	0.276	
4		132¼	Trace	2290		2.10	0.063			2.79	0.276	
3		133¼	0	2250		2.73	0.063			2.63	0.276	
2		131	Trace	2440	300	2.99	0.063		18.7	2.83	0.276	
1	112/84	132¼	Trace	1940		1.77	0.19			2.70	0.585	
								0.945*				0.790*
Labor	112/66	132¼	0	2340	301	1.91	0.19	0.606	16.6	3.17	0.585	0.058
1	106/70		Trace	1150	305	0.861	0.008	0.248	17.4	2.40	0.165	0.124
2	110/74		Trace	1970	312	0.985	0.008	0.267	17.5	3.29	0.165	0.165
3	102/64		+	1870	310	1.34	0.008	0.060	18.8	2.79	0.165	0.287
4			+	2700	315	3.33	0.008	0.060	17.1	3.87	0.165	0.287
5		120¼	++	3470	309	5.46	0.008	0.060	17.5	3.37	0.165	0.287
6	118/74	116½	+	2230	308	1.85	0.008	0.092	18.0	2.90	0.165	0.113
7		115¾	+	2410	326	2.24	0.010	0.092	16.3	3.43	0.318	0.113
8		115¼	++	2120	330	2.67	0.010	0.092	17.7	3.48	0.318	0.113
9		115½	++	1900	325	1.92	0.009	0.092	18.1	2.71	0.378	0.113
10		116	++	2020		1.74	0.009	0.092		3.26	0.378	0.113

*Blood loss at delivery.

TABLE II. CLINICAL DATA WITH SODIUM AND POTASSIUM VALUES IN PATIENT M. G. (CASE 2)

	CLINICAL				SODIUM					POTASSIUM				
DAYS	BLOOD PRESSURE	WEIGHT IN POUNDS	PROTEINURIA GM./LITER	URINE VOLUME C.C./DAY	PLASMA MG. %	URINE GM./DAY	FECES GM./DAY	LOCHIA GM./DAY	MILK GM./DAY	PLASMA MG. %	URINE GM./DAY	FECES GM./DAY	MILK GM./DAY	LOCHIA GM./DAY
13		147½	0	490	310	1.47	0.057			22.4	1.48	0.061		
12		147½	0	620		1.66	0.057				2.35	0.061		
11		147	0	640		1.70	0.057				1.73	0.061		
10		147¾	0	2360		2.38	0.063				3.46	0.506		
9	108/80	147¾	0	1740		1.98	0.063				2.46	0.506		
8		148¼	0	1320		1.92	0.063				2.78	0.506		
7		148¼	0				0.063					0.506		
6		149½	0	2760	321	3.54	0.063			25.6	5.20	0.506		
5		148¼	0	1200		1.67	0.027				2.64	0.144		
4		149	0	1280		1.96	0.027				2.75	0.144		
3		148¾	0	1340		1.63	0.027				2.64	0.144		
2		148¾	0	1460		1.82	0.027				2.69	0.144		
1	114/82	149½	0	1480		1.78	0.027				2.01	0.144		
Labor A		149¾	0	900	322	1.03		0.40*		21.6	1.91		0.30*	
Labor B				195	327	0.25	0.010	0.104		20.1	0.82	0.033	0.051	
1	108/74		Trace	2880	321	3.68	0.010	0.090		17.5	4.01	0.033	0.090	
2			0	2900	321	3.44	0.010	0.092	0.034	19.0	3.75	0.033	0.094	0.015
3	106/70		0	2030	327	1.83	0.010	0.092	0.044	16.8	3.02	0.033	0.094	0.019
4			0	2510	329	2.62	0.010	0.092	0.035	15.9	3.08	0.033	0.094	0.031
5			Trace	1830	320	2.91	0.049	0.068	0.038	16.7	2.87	0.033	0.103	0.029
6	114/78		Trace	3020	316	4.46	0.049	0.068	0.210	17.5	4.20	0.033	0.103	0.152
7			Trace	2200	287	2.23	0.049	0.068	0.148	16.0	2.89	0.033	0.103	0.207
8		128	Trace	1940	311	2.51	0.049	0.072	0.114	20.4	3.72	0.033	0.403	0.236
9		127	Trace	1330	310	1.91	0.049	0.072	0.139	18.3	2.63	0.033	0.403	0.360
10		128		1050	316	1.27	0.049	0.072	0.174	16.8	1.72	0.033	0.403	0.394

*Blood loss at delivery.
Labor A, Until delivery.
Labor B, Remainder of twenty-four hours after delivery.

TABLE III. CLINICAL DATA WITH SODIUM AND POTASSIUM VALUES IN PATIENT M. P. (CASE 3)

CLINICAL					SODIUM					POTASSIUM				
DAYS	BLOOD PRESSURE	WEIGHT IN POUNDS	PROTEINURIA GM./LITER	URINE VOLUME C.C./DAY	PLASMA MG. %	URINE GM./DAY	FECES GM./DAY	LOCHIA GM./DAY	MILK GM./DAY	PLASMA MG. %	URINE GM./DAY	FECES GM./DAY	LOCHIA GM./DAY	MILK GM./DAY
17		122¼	0	860	311	1.28	0.06			25.6	1.00	0.06		
16	114/86	122¼	0	1250		2.20	0.08				1.76	0.11		
15		122	0	1545		1.33	0.08				1.33	0.11		
14	118/80	123¾	0	1315		1.17	0.08				0.73	0.11		
13		122¾	0	985		0.87	0.08				0.56	0.11		
12		122¾	0	965		0.46	0.08				0.51	0.11		
11	112/80	122¾	0	1065		1.43	0.08				1.57	0.11		
10		123¾	0	1775	333	1.22	0.08			23.0	2.54	0.11		
9	112/82	123¾	0	1755		1.88	0.08				2.01	0.11		
8		123¾	0	1935		2.84	0.02				2.67	0.05		
7		123½	0	1610		1.69	0.02				2.36	0.05		
6		123¼	0	2045		2.99	0.02				2.60	0.05		
5		123¼	0	1825		1.87	0.02				2.21	0.05		
4	112/82	123¼	0	1970		2.88	0.02				2.66	0.05		
3			0	1840		3.28	0.02				2.63	0.05		
2 A	114/90		0	1985	368	2.39	0.02			23.4	2.75	0.05		
2 B			0	390		0.98					0.46			
1			0	1750	349	1.57	0.01			24.7	2.30	0.02		
Labor A	136/84		0	205		0.13		0.91*			0.58		0.65*	
Labor B			Trace	1415	337	0.35	0.01	0.19		24.6	2.23	0.02	0.05	
1			0	1580	343	0.21	0.01	0.09		24.2	2.57	0.02	0.02	
2	118/70		0	1390	345	0.15	0.01	0.09	0.01	21.8	2.56	0.02	0.02	0.003
3			0	1945	348	1.84	0.01	0.07	0.01	23.2	2.86	0.02	0.07	0.04
4	128/90		0	1680	343	1.26	0.19	0.07	0.03	21.3	1.60	0.51	0.07	0.17
5			0	2490	357	5.08	0.19	0.07	0.05	21.2	3.60	0.51	0.07	0.32
6			0	2460	345	7.10	0.02	0.05	0.01	21.3	3.03	0.13	0.04	0.29
7			Trace	1395	334	3.71	0.02	0.05	0.02	21.0	2.65	0.13	0.04	0.38
8			0	1515	334	2.89	0.02	0.05	0.06	18.5	2.80	0.13	0.04	0.34
9		111	0	1715	338	3.09	0.02	0.05	0.02	19.3	2.73	0.13	0.04	0.31
10		109	0	1640	332	2.73	0.02	0.05	0.01	21.6	2.34	0.13	0.04	0.32

*Blood loss at delivery.
2A, Before onset of labor; 2B, after onset of labor.
Labor A, Until delivery. Labor B, Remainder of 24 hours after delivery.

TABLE IV. CLINICAL DATA WITH SODIUM AND POTASSIUM VALUES IN PATIENT L. D. TOXEMIA (CASE 4)

	CLINICAL				SODIUM				POTASSIUM			
DAYS	BLOOD PRESSURE	WEIGHT IN POUNDS	PROTEIN-URIA GM./LITER	URINE VOLUME C.C./DAY	PLASMA MG. %	URINE GM./DAY	FECES GM./DAY	LOCHIA GM./DAY	PLASMA MG. %	URINE GM./DAY	FECES GM./DAY	LOCHIA GM./DAY
17	162/116	125½	3.8	1190	337	1.39	0.009		20.9	2.27	0.95	
16	150/114	125¼	4.0	1780		1.89	0.009			2.85	0.95	
15	170/120	126¼	3.2	1830		2.00	0.013			2.91	0.173	
14	160/118	125¾	3.6	1310		1.43	0.013			2.57	0.173	
13	164/110	126¼	3.6	1720		1.89	0.013			2.92	0.173	
12	156/114	126¼	3.6	1560		2.27	0.013			3.06	0.173	
11	150/102	125¾	4.3	1580		1.98	0.013			2.89	0.173	
10	190/120	125½	5.4	1300	339	1.65			23.6	2.81		
9	175/115	125	6.0	1410		1.82				2.97		
8		126	5.4	1540		1.90				2.56		
7		127½	4.0	2080		2.52	0.010			2.50	0.025	
6	158/124	126¼	4.2	1580		2.40	0.010			2.99	0.025	
5	140/110	126¼	4.6	1580		2.44	0.010			3.07	0.025	
4	140/110	127½	4.6	1510		2.32	0.010			2.89	0.025	
3	146/104	126¾	4.2	2120	345	2.65	0.010		22.4	3.20	0.025	
2	140/104	125½	4.2	1810		2.59	0.010			2.86	0.025	
1	140/102	125½	4.4	1510		2.51	0.010			2.89	0.025	
Labor A.	188/118		6.9	160	321	3.95	0.010	0.310*	22.4	0.41	0.025	0.301*
Labor B.	176/118		2.9	1950	318	3.02	0.012	0.284	21.1	2.89		0.392
1	196/128		1.9	3130	319	5.61	0.012	0.223	22.6	3.38	0.144	0.077
2	148/100		1.5	2330	299	4.47	0.012	0.150	18.3	2.47	0.144	0.056
3	148/ 90		2.4	1520	339	2.91	0.012	0.150	28.4	2.41	0.144	0.056
4	140/ 90		2.9	1700	349	2.64	0.012	0.150	21.5	2.37	0.144	0.056
5	146/ 98		1.9	2040	334	2.35	0.012	0.078	24.3	2.34	0.144	0.075
6	122/ 94	108¼	1.7	3020	325	3.42	0.012	0.078	25.0	2.90	0.144	0.075
7	136/102		1.7	2030	326	2.66	0.011	0.078	23.9	2.96	0.078	0.075
8	140/ 80	104¾	1.8	1940	324	3.16	0.011	0.101	22.1	3.20	0.078	0.091
9	126/ 84	104¾	1.2	1520	290	2.64	0.011	0.101	24.5	3.12	0.078	0.091
10	136/ 90	105¼	1.2	1190		1.89	0.011	0.101		3.48	0.078	0.091

*Blood loss at delivery.
Labor A, Until delivery. Labor B, Remainder of twenty-four hours after delivery.

in previously edematous patients is a well-recognized phenomenon (Schwarz and Dieckmann[30]). The potassium again showed a positive ante-partum belance and a less marked tendency to fall after delivery. The potassium curve in fact diverged quite markedly from that for sodium in the post-partum period.

Comment.—The greater sodium loss in the puerperium of this as well as in other pre-eclamptic patients is no doubt due to the disposal of extracellular edema fluid. There was of course no evidence of excessively high ante-partum estrogens or pregnandiol to give an explanation for the greater sodium retention in this patient with toxemia. The period of greatest post-partum sodium loss, however, again closely followed the disappearance of the hormones from the circulation.

RELATION OF SODIUM AND POTASSIUM BALANCE TO CHANGING HORMONE CONCENTRATION IN A TOXEMIC PATIENT WITH INTRAUTERINE FETAL DEATH

A fetal death occurring in the course of the study of a second patient with pre-eclampsia afforded an unexpected opportunity to study the effects produced by diminution in hormone concentrations on the behavior of electrolytes without the complicating factors incidental to delivery (Chart 5).

CASE 5.—M. A. (History No. 125221), admitted Nov. 10, 1938. This patient, a twenty-five-year-old primigravida, gave a history of a last menstrual period on April 15, 1938, and a normal pregnancy observed in the ante-partum clinic until the seventh month. At that time she developed headache and nausea and vomiting with hypertension, proteinuria, and edema. During the hospital stay which followed she improved symptomatically, but the blood pressure level and urinary findings remained unchanged (Table V). The fetal heart was last heard on Dec. 21, 1938, three days before the onset of labor. On December 24 she was delivered of a three-pound macerated stillbirth after a labor of four hours. There was essentially no blood loss and the amniotic fluid had been reduced to a few ounces of thick meconium-like material. The hypertension began to improve on the sixth day, and on the eighteenth post-partum day, the blood pressure reading was 114/78 and the protein in a twenty-four-hour urine was reduced to 1 gm. At her last visit to the follow-up clinic two months after her delivery, the urine was normal and the blood pressure was 120/74.

The hormone assays in this patient revealed changes which may be characteristic of impending or actual fetal death. The estrogens in the urine were relatively low, falling from 900 to 200 rat units per day during the week before fetal death occurred, but persisting as usual in some quantity until about the second post-partum day. Estrogens in the serum were low from the beginning of the study and were practically nondemonstrable in specimens studied two and nine days, respectively, before fetal death occurred. Pregnandiol was present in the urine in traces on the sixteenth and thirtieth days before fetal death, but at other times was apparently absent.

The prolan values were within the normal range, 1,000 to 2,000 rat units per liter for the serum, and 1,000 to 3,000 units for the urine. These findings are in accord with previous observations that estrogen excretion falls much sooner after fetal death than does the prolan.[3, 35]

The sodium balance was positive for the first week of the study, and then was consistently negative until labor occurred. A slight positive balance then developed for two days, after which the fall was resumed until 14.68 gm. had been lost.

The potassium showed an opposite trend, and its steady but slight retention remained unaffected by the fall in hormones, the death of the fetus or delivery. By the end of the study 11.00 gm. had been gained.

TABLE V. CLINICAL DATA WITH SODIUM AND POTASSIUM VALUES IN PATIENT M. A. TOXEMIA (CASE 5)

CLINICAL					SODIUM				POTASSIUM			
DAYS	BLOOD PRESSURE	WEIGHT IN POUNDS	PROTEIN-URIA GM./LITER	URINE VOLUME C.C./DAY	PLASMA MG. %	URINE GM./DAY	FECES GM./DAY	LOCHIA GM./DAY	PLASMA MG. %	URINE GM./DAY	FECES GM./DAY	LOCHIA GM./DAY
32	140/110	127¾	+++	1450	334	2.87	0.01		18.9	2.56	0.02	
31	186/114	127	+++	1585		2.70	0.01			2.44	0.02	
30	146/104	127¼	+++	990		2.42	0.01			2.51	0.02	
29	182/114	127¼	1.4	1675		2.37	0.01			3.01	0.02	
28	174/112	129	2.6	1560		2.58	0.01			2.62	0.02	
27	172/112	129½	2.2	1795		2.83	0.01			2.68	0.02	
26		129¾	2.4	1660		2.61	0.01			2.27	0.02	
25		130	2.6	1440	333	2.93	0.01		25.4	2.73	0.02	
24	158/108	130½	2.8	1450		3.21	0.01			2.75	0.02	
23	146/102	130	2.6	1410		3.84	0.01			3.31	0.02	
22	162/108	130¾	2.2	1850		2.94	0.01			2.65	0.02	
21		130					0.01				0.02	
20	138/ 90	129½	2.0	1735		3.40	0.01			3.00	0.12	
19	164/106	129	2.2	1325		2.58	0.01			2.80	0.12	
18	162/106	129	2.0	1575	303	2.83	0.01		29.3	3.21	0.12	
17	182/114	129½	3.6	1645		3.48	0.01			2.95	0.12	
16	150/102	128¾	3.0	1595		2.41	0.02			2.66	0.33	
15	160/112	129	2.4	1730		2.49	0.02			2.98	0.33	
14	166/116	129¼	2.0	1760		2.31	0.02			2.90	0.33	
13	160/116	129½	2.8	1700		2.90	0.02			2.76	0.33	
12		129	3.0	1660		2.81	0.01			2.42	0.14	
11	164/116	129½	2.4	1830	328	3.26	0.01		25.2	2.48	0.14	
10	158/120	129	2.6	1565		2.83	0.01			2.79	0.14	

9	150/112	129½	2.4	2020		3.14	0.01			3.35	0.14	
8	148/102	129¼	2.4	1550		2.40	0.01			2.75	0.14	
7		129¼	2.0	1815		2.60	0.01			3.23	0.14	
6	152/110	129¼	3.4	1340		2.32	0.01			2.53	0.14	
5	168/138	129½	2.6	1440		2.07	0.10			2.36	0.45	
4	190/120	129¼	3.0	1580	310	2.32	0.10		29.5	2.62	0.45	
3	172/124	129¼	4.2	490	339	1.51	0.10		21.6	1.53	0.45	
2	150/114	129½	2.0	1830	324	1.81	0.10		23.3	2.10	0.45	
1	164/122		2.0	1620		1.70	0.10			1.85	0.45	
Labor A.	170/ 94		2.0	1020		0.93	0.10	0.08*		1.73	0.45	0.09*
Labor B.				80		0.28		0.04*	25.1	0.22		0.05*
Labor C.	146/112			220		0.37		0.06*	24.0	0.96		0.03*
1	140/ 90		3.0	1220		1.32	0.05	0.11	25.3	2.94	0.14	0.03
2	136/ 88		3.0	715	321	0.89	0.05	0.11	26.2	1.81	0.14	0.03
3	132/ 98		2.6	1720	331	2.17	0.05	0.08	25.6	2.06	0.14	0.06
4	140/110		2.6	2550	337	4.38	0.05	0.08	21.2	3.40	0.14	0.06
5	170/110		2.6	2310	329	3.56	0.05	0.08	23.9	2.82	0.14	0.06
6	134/ 96		2.0	2135	336	2.40	0.02	0.04	24.2	2.81	0.12	0.03
7	144/100		1.0	2110	334	2.41	0.02	0.04	24.6	3.10	0.12	0.03
8	120/ 80		1.6	1670	319	2.27	0.02	0.04	23.6	2.76	0.12	0.03
9			1.0	1600	322	2.44	0.02	0.04	23.7	2.67	0.12	0.03
10		120	1.0	1135	326	1.99	0.02	0.04	24.9	2.35	0.12	0.03

*Blood loss in labor and delivery.
Labor A, From beginning of day until onset of labor.
Labor B, From onset of labor until delivery.
Labor C, From delivery until end of day.

Comment.—The loss of sodium in this case began before labor and before fetal death. The only observable trend either in clinical features or laboratory determinations with which it could be correlated was the fall in estrogen and pregnandiol values.

The opposite trend of potassium is difficult to understand. It is perhaps noteworthy that in the other case of toxemia divergence of the curves for the two electrolytes also occurred, but after delivery. In none of the normal cases was this as marked.

RELATION OF SODIUM AND POTASSIUM BALANCE TO HORMONE CONCENTRATION IN A NORMAL PATIENT RECEIVING LARGE DOSES OF ESTROGENS

Conditions the reverse of those associated with fetal death should theoretically be producible by the administration of hormones. In this respect two experiments suggest themselves. First, can sodium retention be increased antepartum by adding to the physiologic hormone supply, and, second, can the usual post-partum loss be prevented by artificially maintaining ante-partum levels?

CASE 6.—M. M. (History No. 119853), admitted Feb. 2, 1939. This patient was a twenty-two-year-old girl in her second pregnancy, which had been entirely normal since her last period on May 23, 1938. After being on a measured intake of sodium and potassium for five days, she was given a total of 180,000 rat units of estradiol benzoate* in six injections on two successive days. There was no evident clinical effect of these injections on the patient. She was spontaneously delivered on June 15 of a six pound, eleven ounce female child after a labor of fourteen hours. The blood loss amounted to 515 c.c.

On each of the first five post-partum days, the patient received two injections of 30,000 rat units each of estradiol benzoate. The breasts failed to enlarge and no milk was available for feeding the baby. Severe afterpains recurred for six days, otherwise the post-partum course was normal.

The nature and quantity of the estrogens injected require some comment. It will be noted that the estradiol benzoate had been standardized in rat units. Therefore the equivalent of about 900,000 international units was injected in the course of forty-eight hours of ante-partum administration and 1,500,000 units during five post-partum days. These amounts appeared comparable to those with which Thorn and Engel obtained their effects on dogs. It must be emphasized, however, that the substance used was the benzoated ester of estradiol, whose effect is slower to develop and more prolonged than is that of the simple hormone. This possibly prolonged effect of the estradiol benzoate should be borne in mind in interpreting the results in this case.

Chart 6 shows that the urinary excretion of estrogen was probably increased for five days during the ante-partum period by these injections and perhaps maintained at a low level for an unusually long period after delivery. The serum estrogen level was unaffected by the estrogen administration and reciprocal effects on the other hormones were not apparent.

Sodium retention in this case was quite marked even before the first estrogen injection, but it continued until term in amounts greater than in any other case. On the fourth post-partum day, there was a loss of sodium, corresponding to that noted in all of the normal cases. Nevertheless, if the entire post-partum period of study is considered, there is evidence of a slight net gain in sodium. This case in which estrogens were administered is the only one in which such a positive balance was present in the post-partum period.

*The estradiol benzoate was in the form of progynon B, supplied by the Schering Corporation through the kindness of Dr. Max Gilbert.

The potassium retention began before the injections were given, was not definitely accelerated by the ante-partum administration of hormone and continued into the post-partum period. It was much more marked than in any other case.

Comment.—The apparently increased ante-partum sodium retention and the positive balance on all but one of the early ante-partum days suggest that the administered estrogens actually had a physiologic effect. The variability in different normal cases makes caution essential before any final conclusion. Nevertheless the difference in the graphs of sodium balance in the case with a dying fetus and falling estrogen curve and this one while hormone was being administered is very striking.

The rise in the potassium curve is difficult to explain. It may have been within the limits of the normal potassium retention of late pregnancy. It is, however, interesting to note that Thorn and Engel[42] did find a little decrease in potassium excretion after the injection of estrone and alpha-estradiol into normal male dogs. In this respect the effect of the estrogens may differ from that of the cortical hormone (Thorn, Engel and Eisenberg[43]).

PLASMA SODIUM AND POTASSIUM

Numerous studies have been made on the sodium and potassium in the serum of normal and toxemic patients. Most of these indicate that no characteristic changes occur (Krebs and Briggs,[21] Denis and King,[7] Stander, Duncan and Sisson[36]). Determinations of sodium and potassium were made by us on plasma samples taken at the time blood was drawn for hormone studies (see Tables I to VI). These were made also to determine whether any alterations in the plasma concentrations of these ions developed in relation to changing hormone conditions.

a. *Sodium.*—The average normal figure for plasma sodium has been given by Kramer and Tisdall[20] as 335 mg., with a range in normal pregnancy of 320 to 362 as found by Denis and King and of 286 to 327 by Krebs and Briggs. Rossenbeck[27, 28] has claimed a fall in serum sodium and a rise in chloride ion in normal pregnancy, with these trends increased in "nephropathia" and "eclampsia." After studying a long series of cases Macciotta[25] has recently reported low sodium values early in pregnancy, but almost normal figures near term. He noted also a conspicuous lowering of plasma sodium on the fourth and fifth post-partum days. The figures obtained in the present study are in general within the normal range. A slight drop in serum sodium on the fifth, sixth, and seventh days corresponding perhaps to the sodium excretion at this time is, however, suggested in several cases.

b. *Potassium.*—The normal figures for plasma potassium have been given by Kramer and Tisdall[19] as 17.9 to 21.3 mg. per 100 c.c., by Truszkowski and Zwemer[46] as 16.7 to 23.0 mg. These are figures offered by the originators of certain methods of determination and those reported by students of conditions in pregnancy have shown a wide range (Krebs and Briggs[2]). It has been in general agreed, however, that no characteristic changes in potassium plasma content develop in either normal pregnancy or pre-eclamptic toxemia, although a single report suggests that the rate of change of serum potassium levels after the injection of potassium chloride is abnormal in the toxemic patient (Szüsz[40]).

The average figures for the uncomplicated pregnancies of this study fell within the normal range, but showed wider fluctuations than are reported for nonpregnant persons. The average values were a little higher and the range of fluctuation still greater in the two patients with toxemia. The high values occasionally obtained were perhaps an error dependent on some hemolysis during the drawing of the blood, perhaps to potassium reaching the maternal circulation from disintegrating cells of an infarcted placenta or dead fetus.

TABLE VI. CLINICAL DATA WITH SODIUM AND POTASSIUM VALUES IN PATIENT M. M. (CASE 6)

	CLINICAL				SODIUM				POTASSIUM			
DAYS	BLOOD PRESSURE	WEIGHT IN POUNDS	PROTEIN-URIA GM./LITER	URINE VOLUME C.C./DAY	PLASMA MG. %	URINE GM./DAY	FECES GM./DAY	LOCHIA GM./DAY	PLASMA MG. %	URINE GM./DAY	FECES GM./DAY	LOCHIA GM./DAY
23		126½	0	990	300	0.58	0.015		22.0	1.24	0.158	
22		125	0	2180		2.81	0.015			4.04	0.158	
21		124	0	1270		0.73	0.015			1.89	0.158	
20		124	0	1655		1.62	0.063			2.08	0.164	
19	100/ 70	123½	0	1635		1.04	0.063			2.34	0.164	
18	106/ 68	124½	0	1530	308	1.39	0.063		22.1	2.32	0.164	
17	108/ 70	124	0	2160		1.51	0.063			2.01	0.164	
16	106/ 70	124	0	1175	310	0.91	0.063		22.1	1.28	0.164	
15	102/ 68	124¼	0	1680	315	1.71	0.063		20.2	2.00	0.164	
14		124	0	2245		2.11	0.020			2.32	0.114	
13	102/ 78	125	0	1205		2.20	0.020			2.33	0.114	
12	92/ 64	125¼	0	1425		1.01	0.020			1.69	0.114	
11	96/ 60	125¾	0	1660	340	0.63	0.020		21.1	1.30	0.114	
10	92/ 60	126	0	1335		0.60	0.013			1.24	0.050	
9	100/ 68	126	0	1410		0.85	0.013			1.06	0.050	
8	100/ 64	125½	0	1770		1.23	0.013			1.81	0.050	
7	92/ 60	124	0	1270	339	0.99	0.013		25.2	1.44	0.050	
6	92/ 56	125	0	1230	345	1.26	0.013		25.7	1.12	0.050	
5	105/ 70	125	0	1250		1.07	0.107			1.53	0.142	
4	95/ 72	125	0	1070		0.27	0.107			0.53	0.142	

3	94/ 78	125½	0	1660		2.18	0.107			2.29	0.142	
2	106/ 78	125¾	0	1420	326	0.63	0.107		22.2	1.25	0.142	
1	106/ 78	125½	0	1325		0.53	0.107			1.12	0.142	
Labor A.	110/ 86	125	0				0.107			1.11	0.142	
Labor B.				964			0.232	1.13*	24.7		0.906	0.79*
Labor C.					335	2.08	0.028	0.234	22.8	0.59	0.101	0.116
1	85/ 50		Trace	1575	329	0.41	0.028	0.254	25.3	2.41	0.101	0.152
2	92/ 58		Trace	1545	325	0.87	0.028	0.254	22.7	2.48	0.101	0.152
3			0	1350	322	1.36	0.028	0.127	20.0	2.41	0.101	0.208
4			0	1680	337	4.60	0.028	0.127	23.4	2.69	0.101	0.208
5	118/ 74		0	1870	335	0.96	0.028	0.127	25.7	2.04	0.101	0.208
6	118/ 74		0	1480	319	1.08	0.026	0.206	26.5	1.92	0.485	0.445
7		114	0	1435	324	1.95	0.026	0.206	27.6	2.07	0.485	0.445
8		113	0	1890	324	2.30	0.026	0.206	23.8	2.73	0.485	0.445
9		114	0	1850	305	2.13	0.026	0.140	21.5	3.21	0.485	0.123
10		113	0	1705	306	0.57	0.026	0.140	21.3	1.71	0.485	0.123
11		112	0	1295	328	0.37		0.140	20.5	1.34		0.123
12		113	Trace	1550	325	0.21		0.045	20.6	1.57		0.042
13		114	0	1700	338	2.34		0.045	20.1	2.13		0.042
14		114	0	1400	336	1.09		0.045	19.7	1.64		0.042

*Blood loss at delivery.

Labor A, From beginning of day until onset of labor.

Labor B, From onset of labor until delivery.

Labor C, From delivery until end of 24-hour day.

FECAL ESTROGENS

The estrogen eliminated in the feces was also estimated in these cases, since it was felt that a potentially disturbed liver function in toxemia cases might influence the rate of excretion of these substances in the bile. The amounts lost by this route were smaller than had been expected from previous reports and no differences were notable in the different types of cases. Loss of estrogens by this means continued for about three days longer than by the kidneys, the additional period probably corresponding to the time required for the products of biliary excretion to be actually eliminated in the stool.

DISCUSSION

The studies which have been presented show that in pregnancy and the puerperium sodium is retained during periods of high estrogen concentration and is lost during periods of diminishing hormones. Potassium is not clearly correlated with hormone change and is in general consistently retained both in late pregnancy and the early puerperium.

That the estrogens are not only correlated with, but are at least one of the causes of the sodium retention seems probable. On the other hand the possibility remains that sodium loss and the fall in estrogen concentrations are simply both associated with some other factor, as for example, another glandular or metabolic change.

The curve of pregnandiol excretion closely parallels that of the estrogenic substances. Progesterone is also reported as capable of causing salt retention, so that the corpus luteum hormone of the pregnant woman may also play a part in the production of edema.

The gonadotropic hormone seems less likely to be involved, particularly because it was observed in Case 5 that while the prolan values remained at about normal levels there was a continuous sodium loss.

The manner in which the estrogens or progesterone may act to prevent sodium excretion can only be guessed at. They may displace sodium into the tissues, prevent its excretion by the kidney, or act through some other gland, as for example the posterior pituitary.

Speculation as to a possible involvement of the adrenal cortex cannot be avoided. In the two cases of toxemia of pregnancy, following delivery in the one and death of fetus of the other, there was a pronounced divergence of the sodium and potassium lines. This could be explained as a return to normal from a previous condition of relatively low potassium and high sodium storage. Such an effect could on theoretical grounds have been produced by hyperactivity of the adrenal cortex.

The relationship of the hormones to the cause of pre-eclamptic toxemia is still evidently a very uncertain one. If the school which believes that sodium is a real causative factor is correct, then the estrogens and perhaps progesterone become a link in the chain of events leading to the appearance of the disease.

Toxemia patients cannot be shown to have an excessive estrogen content of the blood, which by increasing sodium retention might lead to increased edema. It is possible that the low blood and urinary values

for the estrogens should be taken as an indication of high utilization or failure of the conjugation mechanism and hence imply excessive estrogen effectiveness. On the other hand a perhaps more likely explanation is that in susceptible patients amounts of estrogen normally present in pregnancy will lead to the retention of unusual quantities of sodium.

CONCLUSIONS

Evidence has been presented to show that certain of the placental hormones, notably the estrogens, are probably factors in the retention of sodium during pregnancy.

These hormones should then be added to the list of contributing factors, such as high sodium intake and lowered plasma proteins, which may predispose to edema in pregnancy.

So far as water and salt retention are related to either the cause or the symptoms of pre-eclamptic toxemia, the estrogens and perhaps the other placental hormones are also factors.

REFERENCES

(1) *Arnold, J. O., and Fay, Temple:* Surg. Gynec. Obst. **55:** 129, 1932. (2) *Ball, E. G., and Sadusk, J. F., Jr.:* J. Biol. Chem. **113:** 661, 1936. (3) *Bishop, P. M. F.:* Lancet **2:** 364, 1935. (4) *Butler, A. M., and Tuthill, Elizabeth:* J. Biol. Chem. **93:** 171, 1931. (5) *Camp, W. J. R., and Higgins, J. A.:* J. Pharmacol. & Exper. Therap. **57:** 376, 1936. (6) *Coons, C. M., Coons, R. R., and Schiefelbusch, A. T.:* J. Biol. Chem. **104:** 757, 1934. (7) *Denis, W., and King, E. L.:* Am. J. Obst. & Gynec. **7:** 253, 1924. (8) *Frank, R. T.:* The Female Sex Hormone, Springfield, Ill., 1929, Charles C. Thomas. (9) *Freyberg, R. H., and Grant, R. L.:* J. Clin. Investigation **16:** 729, 1937. (10) *Freyberg, R. H., Reekie, D. D., and Folsome, C.:* Am. J. Obst. & Gynec. **36:** 200, 1938. (11) *Gamble, J. L., Ross, G. S., and Tisdall, F. F.:* J. Biol. Chem. **57:** 633, 1923. (12) *Harrop, G. A., and Thorn, G. W.:* Tr. A. M. Physicians **52:** 164, 1937. (13) *Idem:* J. Exper. Med. **65:** 757, 1937. (14) *Harrop, G. A., Nicholson, W. M., and Strauss, Margaret:* J. Exper. Med. **64:** 233, 1936. (15) *Holmes, and Kirk, P. L.:* J. Biol. Chem. **116:** 377, 1936. (16) *Hug, E.:* Compt. rend. Soc. de biol. **127:** 927, 1938. (17) *Hummel, F. C., Sternberger, H. R., Hunscher, H. A., and Macy, I. G.:* J. Nutrition **11:** 235, 1936. (18) *Klodt, Wilhelm:* Arch. f. exper. Path. u. Pharmakol. **186:** 281, 1937. (19) *Kramer, Benjamin, and Tisdall, F. F.:* J. Biol. Chem. **46:** 339, 1921. (20) *Idem:* Ibid. **53:** 241, 1922. (21) *Krebs, O. S., and Briggs, A. P.:* Am. J. Obst. & Gynec. **5:** 67, 1923. (22) *Kurzrok, Raphael, and Ratner, Sarah:* Ibid. **23:** 689, 1932. (23) *Larson, P. S., and Brewer, George:* J. Pharmacol. & Exper. Therap. **61:** 213, 1937. (24) *Levin, Louis, and Tyndale, H. H.:* Proc. Soc. Exper. Biol. & Med. **34:** 516, 1936. (25) *Macciotta, M.:* Riv. ital. di ginec. **21:** 58, 1938. (26) *McGuigan, H. A., and Higgins, J. A.:* Am. J. Physiol. **114:** 207, 1935. (27) *Rossenbeck, H.:* Schweiz. med. Wehnschr. **57:** 1067, 1927. (28) *Idem:* Arch. f. Gynäk. **145:** 331, 1931. (29) *Salit, P. W.:* J. Biol. Chem. **96:** 659, 1932. (30) *Schwarz, O. H., and Dieckmann, W. J.:* Am. J. Obst. & Gynec. **18:** 515, 1929. (31) *Scudder, John, Zwemer, R. L., and Whipple, A. O.:* Ann. Surg. **107:** 161, 1938. (32) *Smith, G. V., and Smith, O. W.:* Surg. Gynec. Obst. **61:** 27, 1935. (33) *Idem:* Am. J. Obst. & Gynec. **36:** 769, 1938. (34) *De Snoo, K.:* Ibid. **34:** 911, 1937. (35) *Spielman, Frank, Goldberger, M. A., and Frank, R. T.:* J. A. M. A. **101:** 266, 1933. (36) *Stander, H. J., Duncan, E. E., and Sisson, W. E.:* Bull. Johns Hopkins Hosp. **36:** 411, 1925. (37) *Strauss, M. B.:* Am. J. M. Sc. **194:** 772, 1937. (38) *Idem:* Ibid. **195:** 722, 1938. (39) *Idem:* Am. J. Obst. & Gynec. **38:** 199, 1939. (40) *Szüsz, Franz:* Zentralbl. f. Gynäk. **60:** 2310, 1936. (41) *Taylor, H. C., Jr., and Scadron, E. N.:* Am. J. Obst. & Gynec. **37:** 963, 1939. (42) *Thorn, G. W., and Engel, L. L.:* J. Exper. Med. **68:** 299, 1938. (43) *Thorn, G. W., Engel, L. L., and Eisenberg, Harry:* J. Exper. Med. **68:** 161, 1938. (44) *Thorn, G. W., and Harrop, G. A.:* Science **86:** 40, 1937. (45) *Thorn, G. W., Nelson, K. R., and Thorn, D. W.:* Endocrinology **22:** 155, 1938. (46) *Truszkowski, R., and Zwemer, R. L.:* Biochem. J. **31:** 229, 1937. (47) *Venning, E. H.:* J. Biol. Chem. **119:** 473, 1937. (48) *Idem:* J. Biol. Chem. **126:** 595, 1938.

DISCUSSION

DR. ARTHUR H. MORSE, NEW HAVEN, CONN.—It is well to consider the experimental work that has preceded the studies here reported. Taylor has referred to the loss of sodium and the retention of potassium in instances of adrenal insufficiency and the reverse of these conditions when cortical hormone is given. In this connection Thorn and Harrop pointed out that the similarity in the chemical structure of corticosterone and the sex hormones indicated the possibility of one or more common physiologic properties, and this prompted the investigation of the possible effect of the sex hormones upon the renal excretion of sodium. Moreover, the prolonged survival of animals adrenalectomized during pregnancy and heat, and the favorable influence of the induction of estrus in adrenalectomized dogs made it appear probable to these investigators that a high concentration of sex hormones is beneficial to adrenalectomized dogs.

Thorn and Harrop found that the injection of 5 mg. of estradiol resulted in a marked and rather prolonged period of decreased sodium excretion in a normal male dog and that this decreased excretion was accompanied by a reduced output of urine. As the effect of the hormone diminished, an increased excretion was noted. Indeed, all the sex hormones so far studied by these authors have displayed some degree of a sodium retaining effect. Estradiol and progesterone proved to be the most active substances in this respect, although pregnandiol was similarly effective.

It appeared to Thorn and Harrop that a possible explanation of the beneficial effect of estrus and pregnancy on the survival of the adrenalectomized bitch might be accounted for on the basis of the salt and water retention induced by the presence of an excess of the sex hormones. Whether this action is direct or mediated through some other endocrine gland is unknown at present.

Later Thorn, Nelson, and Thorn, in a study of the mechanism of edema associated with menstruation, found that the injection of crystalline preparations of estrone, progesterone, pregnandiol, and testosterone induced the retention of sodium, chloride, and water in normal dogs. Balance studies in women demonstrated a retention of sodium, chloride, and water during the intermenstrual as well as the premenstrual phase of the cycle. On the other hand, the onset of menstruation was associated with an increased renal excretion of sodium, chloride and water, while the increased output of estrin at the time of ovulation was associated with a sodium and chloride retention.

Taylor has stated that the greater sodium loss in the puerperium is no doubt due to a disposal of extracellular edema fluid. This has perhaps a parallel in the observations of Zuckerman upon the pigtailed monkey. Zuckerman showed that the process of sexual-skin swelling which occurs in this animal is a physiologically regulated edema. The body weight in the female of the species fluctuates with the phases of the area in question, and when the latter is fully swollen, body weight may be 17 per cent greater than when the skin is inactive. Investigations of daily changes in water metabolism showed that the increase in weight can be largely accounted for by the accumulation and retention of fluid in the sexual-skin area where the water is mainly held. For example, the swollen structure in baboons, when removed at autopsy, may weigh from 10 per cent to 28 per cent of the total body weight. Although some of the water is intracellular, most of the retained fluid appeared to be extracellular, for when the edematous tissue was incised, clear and moderately thick fluid dripped freely from the exposed surfaces. Moreover, when removed at autopsy, frozen, and then sectioned with a knife, the cut surfaces of the tissues were found to be largely made up of crystals of ice.

Zuckerman has shown further that swelling of the sexual skin, which in the pigtailed monkey is present during follicular activity, does not normally occur during the post-ovulation phase of the menstrual cycle. This observation indicates that the progestin produced by the corpus luteum is unable to retain in the tissue in question the water deposited there as a result of estrogenic stimulation in the preovulation phase. A series of experiments carried out on spayed pigtailed macaques which had been first injected with estrone in order to induce the edematous tissue reaction showed that neither testosterone propionate nor cortin was able to prevent

the normal excretion of sexual-skin water once the estrogenic stimulation had ceased. On the other hand, the injection of pitressin at short intervals did delay the subsidence of the swelling.

Although the part played by the hormones in pregnancy is not understood, investigations in the monkey carried out by my laboratory associate, Prof. Gertrude van Wagenen, throw some light on certain phases of the hormonal activity of the placenta. One of these studies relates to the possible hormonal activity of placental tissue left in the uterus following the abdominal delivery of the fetus. Earlier investigations in the mouse and guinea pig have shown that if the fetus is removed but the placenta is allowed to remain in situ, the animal in which this organ is retained persists in its habitus of pregnancy until the afterbirth is delivered spontaneously at the termination of a normal period of gestation. Since gestation in the rodents is comparatively short, a study of the rôle of the placenta in the absence of the fetus, and of placental hormonal activity is more favorably investigated in the monkey in which the duration of gestation is 168 days. In this study van Wagenen removed only the fetus by abdominal hysterotomy. Such a procedure in the monkey gives some technical difficulty since the placenta consists of a primary and a secondary lobe joined by large vessels. Moreover, in early gestation the comparatively heavy musculature of the primate uterus obscures the sites of placental implantation and, if care is not exercised during the operative procedure, uterine contractions are likely to detach the vascular structure. In the group of animals under observation the placenta was retained as long as ninety days without giving rise to external bleeding or to other untoward symptoms. It was then expelled at the termination of the period previously estimated in the case of each monkey for the delivery of a fully matured offspring. The maternal gain in weight occurring during early gestation and the intensification of the sexual-skin coloration persisted until the expulsion of the placenta. Subsequent to the extrusion of this organ there was a loss in body weight exceeding that of the shed placenta and a rapid fading of the coloration of the sexual skin. These findings, together with the fact that lactation was not initiated following the removal of the fetus, suggest that in the monkey the hormonal relationships of pregnancy continue in the presence of the placenta and the absence of the fetus.

Taylor has shown that during pregnancy there is a retention of sodium similar to the retention which Thorn, Nelson and Thorn noted during the intermenstrual and premenstrual phases of the cycle, but that following delivery there is an increased excretion of sodium similar to the increased renal excretion of sodium, chloride and water associated with the onset of menstruation. Finally, he has taken a conservative and, I believe, a wise viewpoint when he indicates that the possible relationship of the estrogenic hormones to the causation of the toxemias is at present not clear. While this possibility must be held in mind, our knowledge of the various hormones and of the interrelationship of the various endocrine glands is still too meager to hazard any definite statement upon this point. On the other hand, investigations of the type just reported will go far in clearing at least some of these vexing problems.

DR. NICHOLSON J. EASTMAN, BALTIMORE, MD.—Evidence of various types is making it clear that the edema, so frequently seen in the toxemias of pregnancy, is conditioned in part at least by an increased avidity of the tissues for sodium chloride. Some years ago Ropp carried out the following experiment: After feeding 5 gm. of sodium chloride to various types of patients, under carefully controlled conditions, he studied the resultant changes in the chlorides of the blood and urine, and from this was able to deduce the fate of the ingested salt. Even in normal pregnancy he found a greater affinity of the tissues for sodium chloride, the blood chlorides augmenting only slightly after feeding the salt, while the urinary excretion was delayed. In toxemias with edema, this was still more marked, so that the ingestion of sodium chloride showed no effect on either the blood or urinary chlorides, *all* of the ingested salt being held by the tissues. Finally, Ropp analyzed edema fluid and showed that after ingestion of salt by edematous pregnant women, the sodium chloride concentration of this fluid was increased.

More recently Richter and Barelare have approached the problem from a different and somewhat unique viewpoint. They studied the nutritional requirements of rats by allowing them to select their own foods. It was found that if presented with a variety of pure substances, such as casein, sucrose, olive oil, sodium chloride, dibasic sodium phosphate, calcium phosphate, calcium lactate, potassium chloride, dried baker's yeast, cod liver oil, wheat germ oil and water, the rats made selections which were conducive to excellent growth and normal reproduction. As soon as the rats became pregnant, however, certain marked differences were noted in the foods they selected. Among the minerals, the most notable alteration observed was a decided increase in the animals' appetite for calcium chloride and sodium chloride. The amount of these substances consumed increased four-fold, whereas other minerals such as potassium chloride were taken in the same quantities as before.

If it be granted that there is an increased affinity of the tissues for sodium in pregnancy, particularly in the toxemias, it is of course important to inquire why. The theme of Taylor's paper is that the estrogenic hormone is probably an important factor. Certain of Taylor's findings surely seem convincing, particularly his results in Cases 4 and 6. In the former, a case of toxemia, the tremendous increase in sodium excretion post partum can only mean that the accumulated concentration of sodium in the tissues of this patient, when suffering from the toxemia, must have been exceedingly high in relation to their concentration in the nonpregnant state. His demonstration in Case 6 that it is possible to maintain a positive sodium balance in the puerperium by administering the estrogenic hormone is a dramatic demonstration that some relationship exists between these two factors, the estrogens and sodium balance. When we come, however, to the question whether the estrogens, through their effect on sodium balance, are responsible for the edema seen in the toxemias of pregnancy, there would seem to be a link missing in the chain. I refer to the fact that in the toxemias, the estrogenic hormone, as is well known, shows abnormally low concentrations both in blood and urine, whereas we would naturally expect, if the above hypothesis is correct, a high one. While this apparent inconsistency does not by any means invalidate Taylor's views, it would seem to require explanation before any *causal* relationship can be postulated between the estrogenic hormone and the edema seen in the toxemias of pregnancy.

DR. WILLIAM J. DIECKMANN, CHICAGO, ILL.—We have been carrying out balance studies for some years, particularly for chlorine, phosphorus, nitrogen, and total salts in the urine. There is undoubtedly a retention of sodium chloride and water in pregnancy which is exaggerated in the pre-eclamptic and eclamptic patient. Which substance is primarily retained we are unable to say at the present time. We had one eclamptic patient whose baby was dead for ten days, but there was no release of sodium, chlorine, or water until the expulsion of the fetus. This is contrary to the findings in one of Taylor's cases.

I wish to report some unpublished data of F. Koch and A. T. Kenyon of other departments of our University. They have complete balance studies for a period of four weeks obtained on two normal males and two normal females. These individuals ate the same food three times a day and for a period of seven days in the middle of the study were given 25 mg. of testosterone daily. There was a significant retention of total nitrogen, inorganic phosphorus, potassium, chlorine, and sodium. Likewise the weight increased. Shortly after the stoppage of the male hormone, there was a negative balance for these various substances. This work fits in very well with the observations made by Taylor.

DR. TAYLOR (closing).—Several of the speakers, particularly Morse, have mentioned other clinical effects that might be produced by the sodium-retaining action of the estrogens. He referred to the increase in weight and the apparent retention of fluid in the sexual-skin of monkeys. The great breast swelling which occurs in some women before menstruation is perhaps merely a storage of fluid in that region, and it is entirely possible that that is due to the premenstrual hormone conditions.

Eastman has put his finger on a very weak point in the hypothesis that the excessive edema in toxemia is an estrogen effect. Most studies show in fact that the estrogenic curves are lower in toxemic patients than in normal pregnancy. This objection can be explained away on various theoretical grounds. The simplest one is to suggest that the low estrogen excretion is evidence of greater utilization by the tissues. This is pure theory, however, and cannot be assigned any importance at present.

Dieckmann cited a case in which the electrolyte changes did not occur in a case of fetal death until after the expulsion of the fetus. It is highly probable that the placenta is differently affected in its hormone activity under various conditions of fetal death. Different reactions on electrolyte behavior would also be expected.

I want it perfectly clear that this is not offered as any new theory of the cause of pre-eclamptic toxemia. It is essentially a study of the cause of what Eastman has described as the increased avidity of the tissues in pregnant women for sodium. I do think, however, that the estrogens and progesterone are the most likely candidates at present to be the cause of this increased avidity of the tissues in pregnancy for sodium, chlorides, and water.

ESTROGENIC AND GONADOTROPIC HORMONES IN THE BLOOD OF CLIMACTERIC WOMEN AND CASTRATES*

C. F. Fluhmann, M.D., and K. M. Murphy, M.D.,
San Francisco, Calif.
(From the Department of Obstetrics and Gynecology, Stanford University School of Medicine)

THIS report deals with the continuation of our study of the estrogenic and gonadotropic hormone content of the blood of climacteric women and castrates and its possible relationship to the production and alleviation of symptoms associated with the cessation of ovarian function (Murphy and Fluhmann[1]).

MATERIAL

A total of 82 patients was available for study. Of these, 25 were climacteric women in whom periodic uterine bleeding was still present or there was a period of less than four months since the last menses (premenopausal); 30 were considered as "postmenopausal" since amenorrhea had existed for more than four months; and 27 were castrates, 23 of whom had had a bilateral oophorectomy and four had had irradiation for some organic pelvic disease. They were all clinic patients, and had applied for treatment because of vasomotor or other disturbances of the climacteric period.

Since the symptom of "hot flushes" is fairly constant and can be expressed numerically, the patients were graded according to the number of flushes occurring each day (Table I). A careful record was kept and, as in our previous study, if only one to five hot flushes were experienced in the course of 24 hours, the patients were regarded as in Grade I, while Grade II consisted of those with five to 10 flushes; Grade III, 10 to 15; and Grade IV, over 15. It is seen from Table I that the more severe types were found in the castrate and postmenopausal groups, while the majority of the premenopausal women belonged to Grade I.

TECHNICAL PROCEDURE

The blood was obtained by venipuncture and sent to the laboratory in a sterile tube. A total of 40 to 50 c.c. of whole blood was necessary to conduct tests for both hormones, and was obtained at either weekly or biweekly intervals.

The tests were performed according to methods developed in the Stanford Gynecological Laboratory and have been described in detail in a number of previous communications (Fluhmann[2, 3]). The gonadotropic hormone was demonstrated by injecting 4.0 c.c. of untreated blood serum into immature mice, and the results judged as in the Aschheim-Zondek test. The amount of blood available was insufficient to do quantitative tests, but it must be remembered that the hormone is not demonstrable in normal women in this manner and therefore a positive result always points to some abnormality.

The estrogenic hormone content was determined by the Fluhmann mucification test,[3] a procedure which gives both qualitative and quantitative results. Although this method has not been widely adopted, our experience attests to its accuracy, and corroboration recently has been received from other laboratories (Soule,[4] Deckert, Mulhall and Swiney,[5] Rakoff.[6]

---

*Read at the Sixty-Fourth Annual Meeting of the American Gynecological Society, White Sulphur Springs, W. Va., May 22 to 24, 1939.

This study was supported in part by the Rockefeller Fluid Research Fund of Stanford University School of Medicine, and by a grant from the Committee for Research in Problems of Sex, National Research Council. Our thanks are due to Mr. John J. Kan, Mr. Pierre Lassègues and Mr. Fred Wong for their technical assistance.

TABLE I. THE DISTRIBUTION OF PATIENTS ACCORDING TO THE SEVERITY OF CLIMACTERIC SYMPTOMS

GRADE	PREMENOPAUSAL		POSTMENOPAUSAL		CASTRATES		TOTAL	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
I	16	64	13	43	7	25	36	44.0
II	8	32	11	37	10	39	29	36.0
III	0		4	13	4	14	8	9.5
IV	1	4	2	7	6	22	9	10.5
Total	25	100	30	100	27	100	82	100

ESTROGENIC HORMONE

A total of 276 tests for estrogenic hormone was conducted in 76 patients, and from three to four readings were obtained in each case. It was possible to demonstrate the presence of estrogen in 65 instances, while the hormone was absent in only 11 (Table II). In keeping with our previous work, these results may be divided into three groups* (Figs. 1 and 2).

1. *Cyclic Estrogen Curve.*—The largest category is composed of patients in whom there is a definite cycle in the appearance of the hormone. At certain intervals a peak approximating the concentration found in the blood of normal women at the time of ovulation is reached, and subsequently the estrogen disappears. The duration of such a cycle is generally about two weeks. This type of curve was noted in 51 patients, 17 of whom were in the premenopausal, 15 in the postmenopausal, and 19 in the castrate groups.

TABLE II. ESTROGEN IN THE BLOOD OF CLIMACTERIC WOMEN AND CASTRATES

GROUPS	NO. OF PATIENTS	NO. OF TESTS	TYPE ESTROGEN CURVE		
			CYCLIC	CONSTANT	NEGATIVE
Premenopausal	22	90	17	4	1
Postmenopausal	27	92	15	6	6
Castrates	27	94	19	4	4
Total	76	276	51	14	11

2. *Constant Estrogen Content.*—In 14 cases, a more or less constant level was found in the amount of estrogen present at each examination (Figs. 1 and 2). At times, only small quantities such as ±3 mouse units† per 100 c.c. of whole blood were found, but in other cases twice that amount or more was present and equalled the peak found at ovulation in most normal women. Of these patients, 4 were in the premenopausal, 6 in the postmenopausal, and 4 in the castrate group.

3. *Negative.*—An absence of estrogen was noted in 11 cases, but it is of interest that only one was in the premenopausal, while 6 were in the postmenopausal, and 4 in the castrate group.

On the other hand, no relationship could be established between the presence or absence of estrogen and the severity of the menopausal symptoms. For instance, 5 negative tests were obtained out of 30 patients in Grade I, 4 of 30 in Grade II, and 2 out of 8 in Grade III.

*This division is based altogether on the series of tests conducted at the time the patients first presented themselves for treatment. In several instances it was possible to make repeated examinations at subsequent periods, some times after treatment and occasionally without any previous therapy. When this occurred, the second series did not always coincide with the original observations. The classification used in the text is correct on the basis of our findings at the present time, but it is possible that with the accumulation of more data, it may be necessary to change our views.

†The "mouse unit" employed in our estrogen determinations is not directly comparable with that given by other investigators. It was standardized with the mucification test, using a pure estrogen in aqueous solution (Fluhmann[3]).

GONADOTROPIC HORMONE

The anterior pituitary hormone content of the blood was determined in 66 patients. Of these, 20 were in the premenopausal, 24 in the

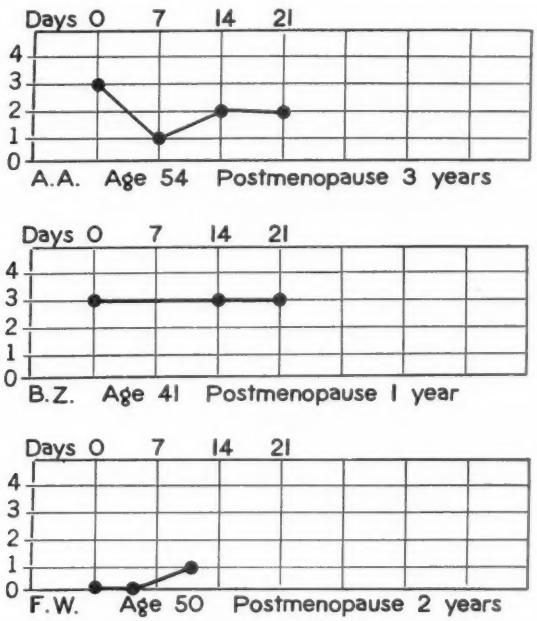

Fig. 1.—Estrogen in the blood of postmenopausal women.

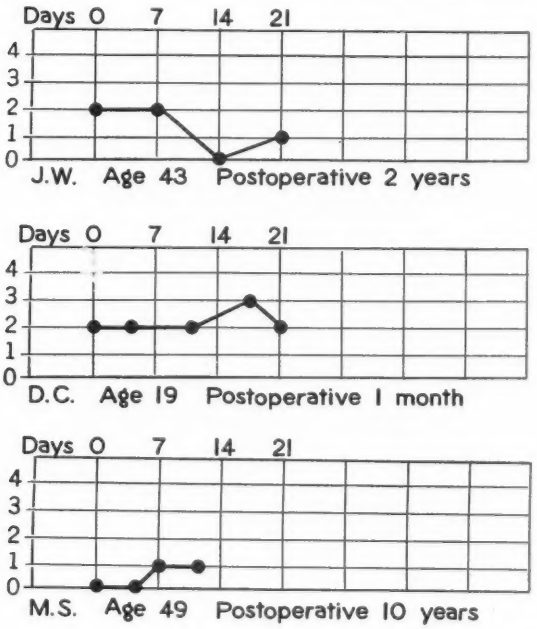

Fig. 2.—Estrogen in the blood of women following castration.

postmenopausal, and 22 in the castrate group. A total of 173 tests was conducted.

The results are given in Table III, and it will be apparent at once that a definite relationship exists between the presence or absence of the hormone and the severity of the hot flushes. This is shown, not only in the total figures for the entire series, but also in each individual group.

TABLE III. GONADOTROPIC HORMONE IN THE BLOOD OF CLIMACTERIC WOMEN AND CASTRATES

GRADE	PREMENOPAUSAL				POSTMENOPAUSAL			
	NEGATIVE		POSITIVE		NEGATIVE		POSITIVE	
	NO.	%	NO.	%	NO.	%	NO.	%
I	9	70	4	30	6	50	6	50
II	2	29	5	71	1	15	6	85
III					0	0	4	100
IV					0	0	1	100
Total	11		9		7		17	

GRADE	CASTRATES				TOTAL			
	NEGATIVE		POSITIVE		NEGATIVE		POSITIVE	
	NO.	%	NO.	%	NO.	%	NO.	%
I	0	0	7	100	15	47	17	53
II	2	28	5	72	5	24	16	76
III	0	0	4	100	0	0	8	100
IV	0	0	4	100	0	0	5	100
Total	2		20		20		46	

In the first place, the highest incidence of positive tests occurred in the groups with the greatest number of patients of Grades II to IV. Conversely, the more patients in Grade I, the fewer the positive tests. For instance, in the premenopausal group, 64 per cent of the women fell in Grade I, and only 9 out of 20 gave positive tests, while in the postmenopausal group the incidence of Grade I was 43 per cent and positive results were found in 17 out of 24 women. Finally, only 25 per cent of the castrates belonged to Grade I and 20 out of 22 consistently showed the presence of increased amounts of anterior lobe gonadotropic hormone in the blood.

Second, an increasing incidence in the number of positive tests is seen when the patients are graded according to the number of hot flushes occurring each day, an observation which holds for all three groups. A total of all the patients shows that positive tests were found in 53 per cent of Grade I, 76 per cent of Grade II, and 100 per cent of Grades III and IV.

EFFECT OF TREATMENT ON HORMONE IN BLOOD

Since a close relationship exists between the presence of unduly large amounts of anterior lobe gonadotropic substances in the blood and the severity of climacteric symptoms, an attempt was made to determine the influence of various methods of therapy on the hormone level. Three small groups were available for this purpose.

1. *Sedatives.*—In our earlier studies the blood was examined at weekly intervals, and during this period of some four or five weeks the patients were given a mild sedative, such as ¼ gr. of phenobarbital every four hours. As might be anticipated, no effect was observed on the concentration of the hormone in the blood. It is interesting, however, that the results bear out the concept that severe climacteric symptoms are associated with increased amounts of anterior lobe hormone. Of 24 patients studied in this manner, 18 gave consistently positive tests while under observation. Ten, or 55 per cent, reported definite improvement from the use of sedation, while 8 reported no change. On the other hand, of 6 patients with negative tests, all were improved to the point that no other method of treatment was necessary.

2. *Estrogenic Hormone.*—The intensive treatment with estrogenic hormones of climacteric patients, resulting in a disappearance of gonadotropic substances in the urine, has been reported by a few observers, notably Albright[7] and Frank and his co-workers.[8] Although our series is small (Table IV), it definitely points to the fact that the general improvement of these patients is not necessarily dependent on the disappearance of the hormone from the blood. The amount of estrogen used in this study, with one exception, was 60,000 I.U. given in divided doses over a period of two weeks. This may be considered inadequate on the basis of the work of Frank

TABLE IV. EFFECT OF ESTROGEN THERAPY ON THE GONADOTROPIC HORMONE CONTENT OF THE BLOOD

PATIENT	TESTS BEFORE TREATMENT				ESTROGEN THERAPY	TESTS AFTER TREATMENT				CLINICAL RESULT
L. A.		+	+	+	Amniotin 60,000 I.U.	0	0	0	0	Not improved
S. R.		+	+	+	Progynon-B 30,000 I.U.	?	0			Improved
A.	0	0	0	0	Progynon-B 60,000 I.U.	0	+	0		Doubtful
H. P.	0	0	0	0	Amniotin 60,000 I.U. repeated—check	0	0	0	0	Improved
R. C.	0	0	0	0	Progynon-B 60,000 I.U.	0	0	0		Improved
J. W.		+	+	+	Progynon-B	+	+			Slight improvement
L. H.		+	+	+	Progynon-B 60,000 I.U.	+	+	?		Improved
G. J.			+	+	Progynon-B 60,000 I.U.	+	+			Improved
F. E.			+	+	Amniotin 60,000 I.U.	+	+			Improved

and others,[8] but nevertheless 6 of the 9 patients were clinically improved and demanded no further treatment. Of the 9, positive tests before treatment and negative afterward were observed in only two instances. One of these patients was improved, and one was not. In 3 cases, tests for the gonadotropic hormone were negative both before and after treatment. In 4 cases, the examination of the blood gave positive tests both before and after the use of estrogenic hormone and all reported relief from distressing symptoms.

3. *X-Irradiation of Hypophysial Area.*—The treatment of menstrual disorders and climacteric symptoms by x-irradiation of the skull has been advocated for many years. A very carefully controlled series of patients was reported from this clinic a few years ago (Newell and Pettit[9]). Since a large proportion of women were improved, it seemed of importance to determine whether this was accomplished by diminishing the amount of anterior lobe hormone in the blood. The roentgen technique employed has been described by Newell and Pettit,[9] but in this study much larger dosages were employed at times, and treatment was directed to the top and

TABLE V. X-IRRADIATION OF THE SKULL AND ITS EFFECT ON THE GONADOTROPIC HORMONE CONTENT OF THE BLOOD

PATIENT	GRADE	TESTS BEFORE TREATMENT			X-RAY DOSAGE	TESTS AFTER TREATMENT				CLINICAL RESULT
E. S.	II	+	0	0	3200 r.	0	0	0		Improved
A. O.	II	0	0	0	770 r.	0	0	0	0	Improved
B. W.	I		0	0	770 r.	0	0			Improved
S. H.	II	+	+	+	3200 r.	+	+	+	+	Improved
V. Z.	IV		+	+	4400 r.	+	+	+		Improved
H. K.	III		+	+	770 r.	+	+	+		Not improved
E. G.	I	+	+	+	1600 r.	+	+			Doubtful

back of the skull as well as over each temple. An extensive epilation occurred on two occasions. It is seen from Table V that in 3 patients tests for gonadotropic hormone in the blood were negative both before and after treatment, and all three reported marked diminution or absence of hot flushes. In 4 instances, the tests remained positive after irradiation, and 2 patients were improved, 1 reported no change, and in 1 the result was doubtful.

DISCUSSION

Since estrogen was demonstrable in the blood of such a large proportion of our patients, it appears that the lack of this hormone is not the primary factor concerned in the production of climacteric symptoms. However, our findings open important questions regarding the production and function of the estrogens and their relation to ovarian activity.*

Estrogenic hormones are not demonstrable in the blood during early life. They first make their appearance at about the age of eight years, when the secondary sexual characters begin to develop (Fluhmann[3]). In adult life, they are found at cyclic intervals and generally accompany certain specific events of the menstrual cycle. These observations point to a close relationship with the function of the ovaries, but leave us in the dark as to the significance of the estrogens in the absence of the gonads. They must have an extragonadal origin, and the adrenals have been suggested as the probable organ responsible for their production (Parkes[11]). However, another unexplained observation in castrates and in patients after the menopause is the atrophy of the accessory sexual organs which occurs in spite of the presence of the hormone. It is possible that the ovaries do not produce estrogenic substances at all, but merely utilize them or change them into a more active form which can act on the uterus and vagina. A second possibility is that there is only *one* true "ovarian hormone" and that the substances found in the blood after the gonads are removed are by-products of cholesterol metabolism which are capable of inducing changes in the rodent vagina but not of maintaining the integrity of the human accessory genital organs.

The association of climacteric symptoms with an increase of gonadotropic substance in the blood or urine is not a new observation. It

*Since our studies were made in patients with symptoms, the criticism may be advanced that they cannot be considered as representing normal climacteric women. In a recent report, however, Shute[10] found that estrogen was demonstrable in the blood of a large percentage of postmenopausal patients, and that the presence or absence of symptoms did not alter the incidence of positive tests for the hormone.

was first made by one of us (Fluhmann[12]). Zondek[13] later described the endocrine changes of the climacteric as occurring in a definite order, stating that his hormone studies of blood and urine indicated three stages: first, a period of excessive estrogen production; second, an absence of estrogen; and third, a hypersecretion of gonadotropic hormone with a total absence of estrogen. This statement, not supported by protocols or detailed experimental evidence, has been widely quoted, nevertheless, in medical literature. It never has been substantiated, and an analysis of our own observations from patient to patient fails to bring corroboration. In a noteworthy contribution, Albright[7] drew attention to overproduction of gonadotropic substance and the occurrence of hot flushes. He demonstrated that persistent estrogenic therapy which diminished the excessive excretion of gonadotropic factors, usually brought about a general improvement of the patient. Frank and others[8] following an extensive investigation, reached essentially the same conclusion.

It is difficult to compare our findings directly with those of investigators who base their endocrine tests on biologic changes in laboratory animals injected with material which they obtain from blood or urine by a prolonged chemical extraction. However, our studies lead us to believe that there is a distinct relationship between the severity of climacteric symptoms and the occurrence of abnormal quantities of gonadotropic anterior lobe hormone in the blood. A further analysis of our results makes us feel that we are not dealing with a "cause and effect" problem. Severe symptoms and positive blood tests appear concurrently, but the findings in women treated in various ways indicate that clinical improvement may be obtained while large amounts of the hormone are still present in the blood. It is known also that excessive amounts of gonadotropic factors are excreted in the urine many years after climacteric symptoms have disappeared. It seems more logical, therefore, to infer that the symptoms and the overproduction of the hormone both result from a common basic cause rather than that the activity of the anterior hypophysis is directly responsible for the complaints characteristic of the climacteric epoch. If this is so, the value of routine employment of blood or urine tests as a therapeutic index becomes doubtful. However, because of the well-recognized effect of autosuggestion in the treatment of these patients and the difficulty of correctly evaluating clinical results, it is hard to give a precise answer.

CONCLUSIONS

Examination of the blood of climacteric women and castrates revealed that, in general, failing or absent ovarian function is not associated with a complete disappearance of substances having estrogenic properties when injected into spayed rodents. The hormone may be detected at cyclic intervals or it may be constant, but no relationship between climacteric symptoms and its absence or presence could be established.

The presence of excessive amounts of a gonadotropic substance probably of anterior hypophysial origin was found in the blood of women

of the climacteric age and after castration. It bears a distinct relationship to the severity of so-called climacteric symptoms. Clinical improvement of such patients was observed following treatment with sedatives, estrogen, or X-irradiation of the skull, while unduly large amounts of gonadotropic substances were consistently demonstrable in the blood.

REFERENCES

(1) *Murphy, K. M., and Fluhmann, C. F.:* West. J. Surg. **46:** 451, 1938. (2) *Fluhmann, C. F.:* Am. J. Obst. & Gynec. **20:** 1, 1930. (3) *Idem:* Endocrinology **18:** 705, 1934; Am. J. Obst. & Gynec. **32:** 612, 1936. (4) *Soule, S. D.:* Am. J. Obst. & Gynec. **35:** 309, 1938. (5) *Deckert, E. F., Mulhall, E., and Swiney, C.:* J. Lab. & Clin. Med. **23:** 85, 1937. (6) *Rakoff, A. E.:* Proc. Soc. Exper. Biol. & Med. **40:** 195, 1939. (7) *Albright, F.:* Endocrinology **20:** 24, 1936. (8) *Frank, R. T., Goldberger, M. A., and Salmon, U. J.:* N. Y. State J. Med. **36:** 1363, 1936. (9) *Newell, R. R., and Pettit, A. V.:* Radiology **25:** 424, 1935. (10) *Shute, E.:* Endocrinology **24:** 744, 1939. (11) *Parkes, A. S.:* Lancet **2:** 902, 1937. (12) *Fluhmann, C. F.:* J. A. M. A. **93:** 672, 1929; Calif. & West. Med. **35:** 279, 1931. (13) *Zondek, B.:* Klin. Wchnschr. **9:** 393, 1930.

Stanford University Hospital

DISCUSSION

DR. EMIL NOVAK, Baltimore, Md.—Fluhmann has made reference to the early work of Zondek on the hormone conditions of the menopause. You will recall that Zondek spoke of three phases, viz., hyperfolliculinism, hypofolliculinism, and polyprolanism, the last-named persisting for many years after the menopause. This view of the endocrine sequence of events at the menopause has had to be modified in various ways, and there are no doubt individual differences in different women. The frequent persistence of estrogen for many years after the menopause is now well established. Fluhmann has shown that this persisting estrogenic hormone may exhibit cyclical variations, and this may have a bearing upon the not infrequently periodic nature of vasomotor exacerbations in the menopausal years.

While the postmenopausal persistence of gonadotropic principles is well recognized, it seems clear that this excess cannot in itself cause the menopausal symptoms, for it commonly persists long after the disappearance of such symptoms. It is not surprising, therefore, that Fluhmann finds that estrogenic therapy frequently relieves the symptoms, even though the gonadotropic hormone still persists. In a small number of cases, Bennett in our laboratory has found that even the implantation of estrogenic pellets of considerable strength will not always bring about disappearance of the gonadotropic hormone, though the symptoms are relieved.

Studies of this sort indicate to my mind that imbalance of opposed hormones is more frequently the cause of clinical symptoms than is mere quantitative excess of one hormone. This point can be illustrated in various ways. A good example is primary dysmenorrhea, which so often begins not at puberty, but a short time later, i.e., when ovulation and corpus luteum formation begin. Before this in many girls only estrogen is present, but dysmenorrhea is not noted until the imbalance between this and the corpus luteum becomes operative. Again, dysmenorrhea is rarely seen in the functional bleeding of middle life, when again estrogen is present without progesterone. And other examples might be adduced.

EXPERIMENTAL BIOLOGICALLY ACTIVE OVARIAN TUMORS IN MICE*

Histogenesis and Relationship to Similar Human Ovarian Tumors

Samuel H. Geist, M.D., Joseph A. Gaines, M.D., and Abou D. Pollack, M.D., New York, N. Y.

(From the Gynecological Service and the Department of Laboratories of The Mount Sinai Hospital)

OVARIAN tumors possessing biologic activity have been produced by the roentgen irradiation of mice. Such tumors exhibit a striking similarity to those human ovarian neoplasms which produce estrogenic effects; namely, the granulosa cell tumor and its more luteinized variations, and the theca cell tumor. Much has been written in the last decade concerning both the structure and origin of these human ovarian tumors and their hormonal significance. There is still, however, considerable speculation in regard to their histogenesis and the relationship they bear to each other.

Studies of serial sections of the ovaries of irradiated mice have made available to us a material from which certain conclusions can be drawn regarding the development of these neoplasms. This experimental investigation may also afford a key to a more fruitful consideration of their counterparts in the human being.

METHODS AND MATERIALS

All the experiments were carried out with white, female mice of an inbred, homogeneous stock. At the time of irradiation the mice were approximately five to six weeks old (puberty). Two hundred mice were irradiated while 35 were kept as controls. Each mouse received 200 r., measured in air, in a single dose. The irradiation factors were 180 kv., 8 ma., 50 cm. distance, 0.5 mm. Cu. filtration for one group and 200 kv., 20 ma., 50 cm. distance, 1.0 mm. Cu. filtration for a second group.†

The incidence of ovarian tumors subsequent to roentgen radiation has already been charted for several strains of white mice by Furth and Furth.[8] We were primarily interested in the histogenesis of these tumors. Therefore, most of the mice which died spontaneously were ignored in this study. It was felt desirable to use mice which could be autopsied immediately on being killed in order to insure the minimum of post-mortem change. Complete autopsies were done.

One hundred seventeen mice were studied in this series. For the early changes after irradiation at least one mouse was killed and examined each day during the first seven weeks. There were 55 mice in this group. During the period from seven weeks to ten months, 24 mice were examined at intervals. And finally, during the period from ten to fifteen months, 38 mice were similarly examined.

Of the 38 mice in the last group 22 exhibited ovarian tumors of various types.

*Read at the Sixty-Fourth Annual Meeting of the American Gynecological Society, White Sulphur Springs, Va., May 22 to 24, 1939.

†The irradiation was carried out in the Department of Radiotherapy of The Mount Sinai Hospital through the kindness of Dr. William Parris and with the cooperation of Dr. Louis Zaretzki.

LITERATURE

The effects of x-rays upon the ovaries of mice were described in detail by Brambell, Parkes and Fielding,[1-5, 19, 20] in a series of studies beginning in 1927. Irradiation of immature female mice resulted in primary degeneration of the ova, followed by complete disintegration of the follicle structure. The interfollicular tissue was replaced by cords of luteallike cells which were interpreted as having originated from proliferations of the germinal or surface epithelium. A second proliferation was described in some cases in which a folliculoid arrangement of cells was noted. In mature mice, the ova were likewise destroyed but no post-irradiation proliferations from the germinal epithelium were observed. Instead, the tissue composing the sterilized ovaries after two and one-half months was described as having been derived from persistent and growing membrana granulosa cells and the interfollicular elements of the ovarian cortex.

The fat-containing, luteallike cells which finally replace the ovarian parenchyma in irradiated mice are of particular interest and will be fully considered below.

It was further found that in irradiated immature mice that reached maturity, the estrus cycle was not suppressed. In other words, even after destruction of the follicle apparatus, sufficient estrogenic hormone was elaborated to produce extra-ovarian changes of estrus. When, however, a bilateral oophorectomy was performed, estrus ceased, indicating that the parenchyma of the ovary was responsible for the production of the estrogenic effect.

Furth and Furth[8] found while studying the effects of x-rays that the incidence of ovarian tumors in irradiated mice kept to senility was 15 times that in control stocks. In an analysis of these neoplasms by Furth and Butterworth[9] two main types were evident: (1) Tubular adenomas, arising by proliferations of the surface epithelium in the form of epithelial canals, and (2) granulosa cell tumors, derived from the cell nests formed from normal follicles following degeneration of the ova. Traut and Butterworth[23] also suggested that these granulosa cell neoplasms were derived from surviving granulosa cells in the x-rayed mice.

HISTOLOGIC CHANGES IN MOUSE OVARY FOLLOWING IRRADIATION

Following irradiation of mature mice the histologic changes noted within the ovaries pursue a definite pattern. Arbitrarily, these changes may be divided into three stages, each of which presents characteristic features. It must be emphasized, however, that they are not sharply demarcated but are continuous one into the other. A résumé of these postirradiation effects is presented for a better understanding of the evolution of the tumor growths.

STAGE OF FOLLICLE DESTRUCTION

The surface epithelium shows no changes during the early months. It persists as a single layer of cuboidal cells without evidence of proliferation. The tunica albuginea likewise plays no active role, appearing as a thin, compressed, fibrous sheath.

All primary oocytes show evidence of degeneration within the first two days after irradiation. The normal cell structure of these ova is quickly effaced, leaving only remnants of a shrunken, collapsed zona pellucida. Though eventually absorbed, these degenerated remnants persist for many weeks, their detection being especially apparent with the Mallory stain. The ova within the medium-sized and larger follicles show greater resistance. Some degree of degeneration is, however, apparent in all of them by the second week.

Degeneration within the granulosa cells of the follicles progresses at a slower rate. Greater follicle destruction is noted where the ovum has previously been affected. Wherever mitotic activity among the granu-

losa cells is noted, examination of serial sections discloses a fairly well-preserved ovum. This would seem to indicate a delay in follicle destruction rather than a proliferative effect due to x-ray. Though some necrosis of granulosa cells occurs early, follicular atresia is not complete until about the seventh week. "Anovular follicles" within the cortex of the ovary at this stage refer to the single-layered follicles in which the ovum has disintegrated, leaving a circular or folliculoid arrangement of cells. They are of interest especially because some of them may persist long after the larger follicles have disappeared. They show no evidence of growth, however, and their role is not of significance.

The theca interna is not destroyed by the irradiation. It begins to proliferate about some of the follicles as early as the first week. The theca interna is represented by several layers of plump, epithelioid cells arranged in a circumferential manner around the degenerating follicle, and merges indistinctly with the surrounding parenchyma. Their nuclei are large, ovoid and vesicular, with occasional mitotic figures. It is of critical importance that the granulosa cells do not participate in this proliferation. Occasionally, areas are found in which proliferating theca interna cells merge imperceptibly with the surrounding tissue. Moreover, the line of demarcation between granulosa and theca cells may be obscure. It is thus possible to mistake proliferating theca cells for persisting and proliferating granulosa cells. Serial sections disclose, however, that this picture is produced by tangential section through the proliferating theca about a degenerating follicle, since deeper sections reveal a distinct demarcation between granulosa and theca (Fig. 2). Further contrast between theca and granulosa cells is made possible by differential stains (Mallory and Masson). These bring out the fine connective tissue strands among the theca interna cells and their absence among the granulosa cells.

The interfollicular tissue of the ovary begins to show evidence of change during the third and fourth weeks after irradiation. At this time one can detect an increase in the size of the parenchymal cells and a tendency to be separated into rounded groups or elongated cords by thin strands of connective tissue. The cytoplasm acquires a foamy appearance, and the nuclei appear larger, paler, rounder, and more vesicular. With succeeding weeks this luteinization of the parenchyma becomes more apparent, progressing as the follicles show increasing degeneration. The proliferating theca interna likewise shows evidence of slight luteinization and tends to become indistinguishable from the surrounding tissue.

Corpora lutea, when present, appear to be well preserved. In one instance, fifty-five days after radiation, section of an ovary showed a complete disappearance of all follicles, slight but diffuse luteinization of the parenchyma and the persistence of a well-preserved corpus luteum. Although it is possible that ovulation may occur a few days after irradiation,[20] it does not occur at this late date. The corpus luteum differs from the remainder of the ovary in that it consists of a single, rounded, well-demarcated mass, in which the individual cells show round, uniform nuclei and more homogeneous, acidophilic cytoplasm.

To recapitulate, then, the ovaries of mice x-rayed at puberty show definite changes during the first six or seven weeks (Fig. 1*A*). The surface epithelium and tunica albuginea appear unaffected. The primary oocytes and then the ova of large follicles are quickly destroyed.

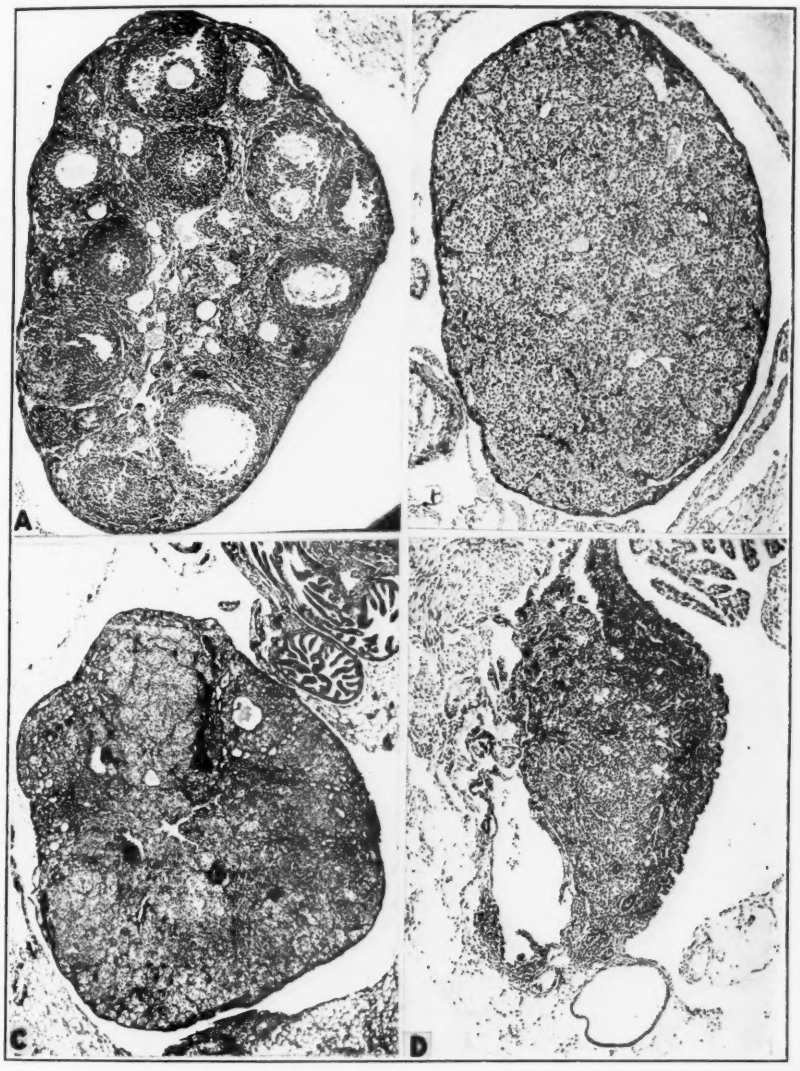

Fig. 1.—Mouse ovaries. Postirradiation changes. *A*, Stage of follicle destruction. *B*, Stage of luteinization. *C*, Stage of tubular downgrowth from surface epithelium. *D*, Ultimate atrophy of ovary and partial replacement by downgrowing surface epithelium.

The granulosa cells degenerate progressively but more slowly. The theca interna proliferates and along with the interfollicular parenchyma receives a luteinizing stimulus. Corpora lutea are apparently not destroyed and perhaps persist because of the same luteinizing stimulus which affects the parenchyma.

STAGE OF LUTEINIZATION

By the sixth or seventh week after irradiation, the ovaries present a picture of almost complete luteinization (Fig. 2*B*). The entire ovary is replaced by a diffuse mass of enlarged polygonal or rounded cells with distinct, vesicular nuclei, and abundant, foamy cytoplasm. These are arranged into irregular groups by thin strands of connective tissue. The only residue of the follicle system are scattered, small, cystic spaces, containing crumpled remnants of zona pellucida. Although in the normal mouse ovary the bulk of tissue is made up of follicular structures, the luteinized ovaries are not smaller than normal. The space previously occupied by the follicles is compensated for by the enlargement of the parenchymal and theca cells through luteinization. Although

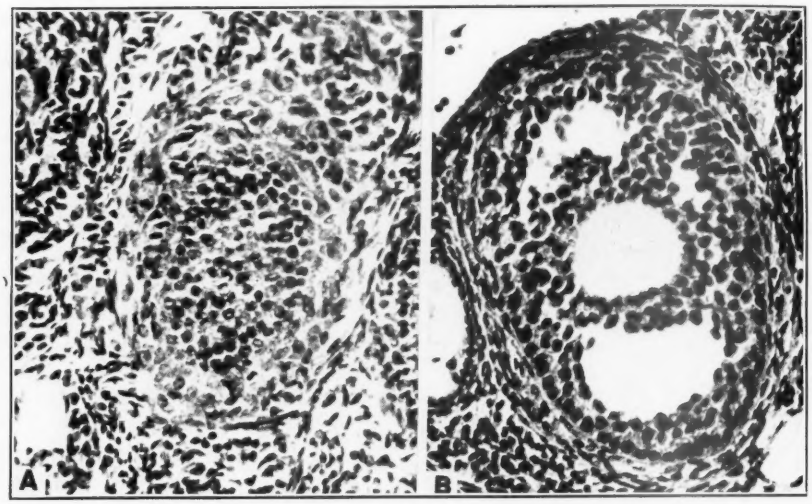

Fig. 2.—Ovary four days after irradiation. *A*, Tangential section through periphery of follicle showing proliferation of granulosa and theca interna cells suggesting the merging of both with the parenchyma. *B*, Serial section through same structure at deeper level shows, however, distinct demarcation between granulosa and theca interna and parenchyma.

proliferation of the luteinized cells is not conspicuous, that such did occur is indicated by the presence of occasional mitotic figures. At the periphery of the ovary the surface epithelium and tunica albuginea appear unchanged. In the outer cortex an occasional folliculoid arrangement of parenchymal cells is noted together with the previously mentioned inactive, "anovular follicles." Ovaries examined during the third, fourth, and fifth months show little change beyond variations in the quantity of luteinization and evidence of partial degeneration of small groups of luteinized cells. The excessively large, foamy, lutein cells may represent evidence of functional exhaustion, comparable to that seen in the human corpus luteum. It is to be emphasized that the uterine mucosa in these cases shows proliferation. The vaginal epithelium exhibits good layering, cornification and mucification. These findings are in agreement with the observations of Parkes[20] who found that in x-rayed mice estrus phenomena could be demonstrated.

STAGE OF PROLIFERATION OF THE SURFACE EPITHELIUM

After the sixth month, an additional phenomenon is noted in practically all cases. The surface epithelium becomes more columnar and shows evidences of proliferation (Fig. 1*C*). Numerous small tubular downgrowths penetrate the cortex of the ovary. Though at first confined to a small crescent or thin layer at the periphery, in the older mice this surface proliferation becomes more conspicuous. The glandlike downgrowths are often convoluted so that an adenomatous picture is created. The dark-staining epithelial cells which make up the new growth in the cortex of the ovary show occasional mitoses. In many instances the ovary is found to be composed of a medullary portion of lutein cells with partial degeneration and a surrounding cortical layer of tubular, adenomatous, epithelial tissue.

The ultimate picture in this series of changes, if tumor growth does not occur, is represented by Fig. 1*D*, obtained from a mouse fifteen months after irradiation. The ovary appears shrunken and small. The surface epithelial proliferation which had at first encircled the partially degenerating lutein cells, completely replaces this structure. The final result is that of a small cellular body composed of irregularly distributed, dark-staining, epithelial cells with occasional glandlike formations. No fat is demonstrable in the latter, nor are they accompanied by estrogenic effects.

DESCRIPTION OF OVARIAN TUMORS

Of those mice that were killed in the period of ten to fifteen months after irradiation, 22 showed the presence of unilateral or bilateral ovarian tumors. The largest of these was 2.5 cm. and the smallest a few millimeters in diameter. Most of the tumors had a yellowish color, and some grayish. Partial degeneration and hemorrhage were occasionally noted grossly. Only those new growths were considered tumors in which the proliferation obviously obliterated the essential architecture of the ovary.

Two main types of tumors were found: a tubular adenoma, originating from the surface epithelium, and parenchymal lutein tumors derived from the ovarian parenchyma. The former have no hormonal implications, while the latter show definite estrogenic effects.

For purposes of simplification, we shall consider the parenchymal tumors in three categories; namely, a granulosa cell type, a thecalike cell type, and a lutein cell type. Actually, none of these is found pure except an occasional completely luteinized form. In 5 cases the granulosa cell dominated the tumor. In only one of the neoplasms did the predominating cell simulate those of the theca interna. Both the granulosa and thecalike tumor cells contain small amounts of doubly refractile fat. The remaining tumors, in which luteinization becomes extreme, are classified as the lutein cell type only on the basis of a quantitative difference in fat content.

Granulosa Cell Type.—Mouse 7-8. Killed thirteen months after irradiation. The left ovary was replaced by a spherical, smooth, grayish yellow tumor measuring 2.5 by 2.5 by 2 cm. (Fig. 3). The right ovary was minute, otherwise not unusual.

The uterus and uterine horns were moderately enlarged. A vaginal smear taken several days before death showed an estrogenic effect.

On microscopic examination the tumor was composed of cell masses and thick cell cords separated by delicate connective tissue and blood vessels. Most of the cells had an epithelial appearance and resembled the granulosa cells of the normal follicle. The nuclei were mainly small and dark. The cytoplasm was moderate in amount and basophilic or neutrophilic in staining reaction. The cytoplasm was finely vacuolated and contained fat which was doubly refractile through the polariscope. Mitoses were frequent; the tumor appeared to be actively proliferating.

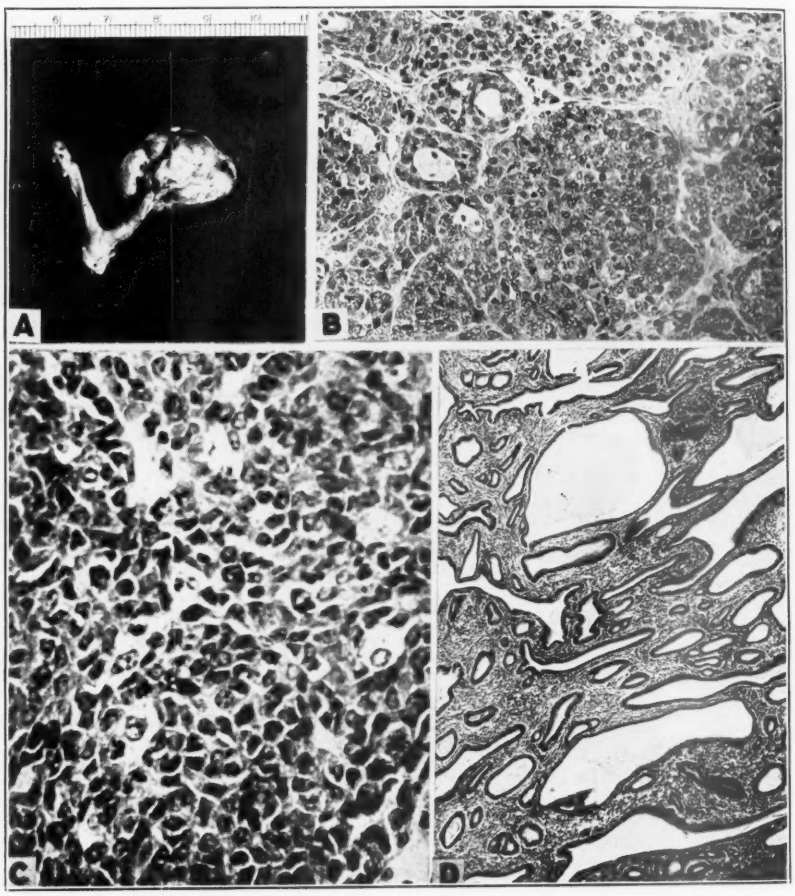

Fig. 3.—Mouse 7-8. Parenchymal lutein tumor of the granulosa cell type. *A*, Gross appearance of tumor in left ovary. Enlargement of uterine horns. *B*, Microscopic appearance of tumor (low power). *C*, Same (high power) showing resemblance of cells to those of granulosa. Several mitotic figures seen. *D*, Cystic hyperplasia of uterine endometrium.

In some areas the cells were larger, more elongated, and had more vesicular nuclei. These cells resembled more the theca interna cell of the normal ovary. Many cells were much larger and more irregular with hyperchromatic nuclei and even with atypical mitoses (tripolar). In some cells the cytoplasm appeared quite foamy, giving the impression of more marked luteinization. The uterine endometrium showed cystic hyperplasia. The vaginal epithelium showed good layering, cornification and mucification.

Thecalike Cell Type.—Mouse 4-6. Killed fourteen months and nine days after irradiation. The left ovary was the site of a whitish tumor 0.9 cm. in diameter (Fig. 4).

Microscopically, a small crescent of ovarian tissue was found. The tumor was composed of large sheets of cells arranged in streams in the fashion of nonepithelial, rather than epithelial cells. The cells were elongated with large, oval, rather vesicular nuclei and had an ill-defined, slightly vacuolated, eosinophilic cytoplasm. They resembled the cells of the theca interna showing early luteinization. Mitoses were moderate in number. Some portions of the tumor exhibited smaller, rounder cells resembling more the granulosa type. Most of the cells showed some degree of luteinization. The fat they contained was anisotropic. Scattered throughout were typical large foamy lutein cells.

The endometrium showed moderate proliferation.

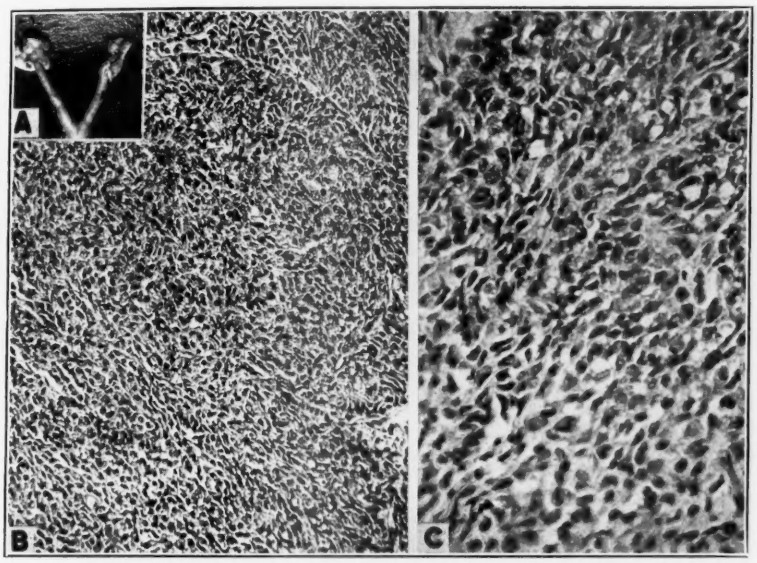

Fig. 4.—Mouse 4-6. Parenchymal lutein tumor of the thecalike cell type. *A*, Gross appearance of tumor in right ovary. Slight enlargement of uterine horns. *B*, Microscopic appearance of tumor (low power). *C*, Same (high power) showing resemblance of cells to those of theca interna.

Lutein Cell Type.—Mouse 4-2. Killed sixteen months, eleven days after irradiation. The left ovary contained a round yellow tumor measuring 0.4 by 0.5 cm. (Fig. 5). The right ovary was small. The uterus and uterine horns were thick.

On microscopic examination, the great part of the left ovary was replaced by confluent nests of large luteinized cells having a foamy, eosinophilic cytoplasm. The cortex of the ovary still persisted as a thin shell of small, dark spindle cells compressed against the tunica albuginea. At one pole of the ovary the germinal epithelium had grown down into the tumor in the form of tubules and glandlike structures, the cells of which retained the appearance of the surface epithelium.

The right ovary presented an undifferentiated parenchyma into which there had been an extensive downgrowth of tubular germinal epithelium. In addition there were sporadic, small nests of large, foamy cells.

The endometrium presented an extensive cystic hyperplasia. The vaginal epithelium was markedly thickened, with conspicuous cornification.

It must be stressed again that the tumors just described have been chosen out of the entire group because each represents an extreme development in one direction or another. Actually the granulosa cell and theca cell differentiations proceed side by side within the same tumor. In addition, luteinization becomes superimposed on both lines of cellular differentiation and reaches its highest intensity in the lutein type of tumor.

In short, the evolution and definitive structure of each of the tumors is dependent on a dichotomous growth tendency from a single undifferentiated stem cell—the parenchymal cell of the ovary. The ultimate luteinization varies quantitatively and is superadded.

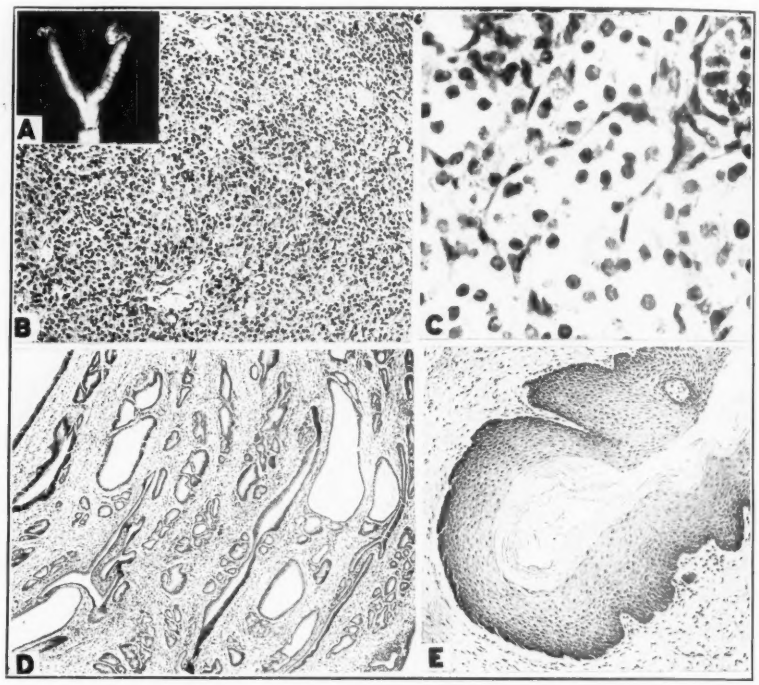

Fig. 5.—Mouse 4-2. Parenchymal tumor of the lutein cell type. *A*, Gross appearance of small tumor in left ovary. Enlargement of uterine horns. *B*, Microscopic appearance of tumor (low power). *C*, Large luteinized cells with foamy cytoplasm containing anisotropic fat. *D*, Cystic hyperplasia of endometrium. *E*, Proliferation of vaginal epithelium with cornification.

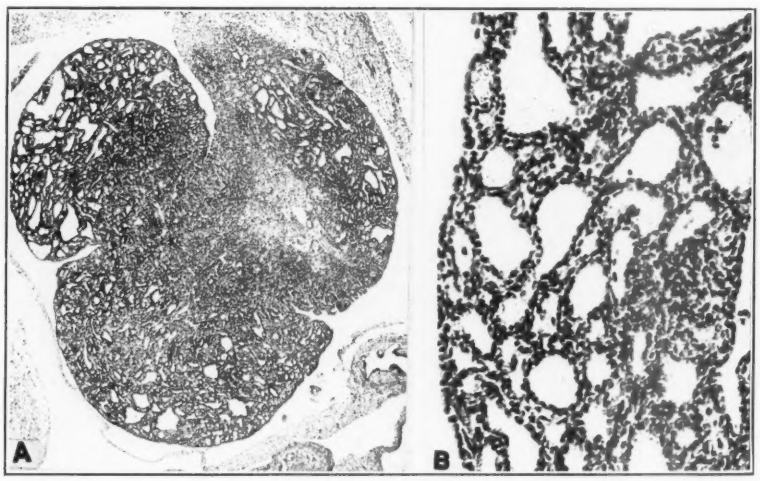

Fig. 6.—Mouse 3-10. *A*, Tubular adenoma arising from proliferation of surface epithelium. *B*, The tubular downgrowths form cystic glandlike structures.

Tubular Adenoma.—Mouse 3-10. Killed fourteen months, twenty-three days after irradiation. One ovary measures 0.3 by 0.3 cm. (Fig. 6) and the other 0.1 by 0.2 cm. Uterine horns are not enlarged. Vaginal smears over a period of several days before death were of the anestrus type.

In both ovaries tubular and glandlike, downward proliferations of the surface epithelium have almost entirely replaced the ovarian tissue. The cells of these downgrowths are similar to those of the germinal epithelium. Some glands have undergone cystic dilatation. Infrequent mitoses are found. Occasional degenerating luteinized parenchymal cells are noted.

The endometrium shows slight proliferation. The vaginal mucosa is atrophic.

HORMONAL ACTIVITY IN PARENCHYMATOUS LUTEIN TUMORS OF MICE

The biologic activity of these neoplasms is expressed by the effect produced upon the uterus and vagina. The quantitative response does not depend upon the size of the tumor or extent of luteinization. The endometrium of the uterus shows distinct evidence of proliferation, often to the extent of cystic hyperplasia. The vaginal mucosa in several instances show a full proliferative effect, with thickened epithelium and cornification. Others present surface mucification. Only occasionally is a full estrus vaginal smear obtained. Several attempts were made to transplant portions of the granulosa cell type of tumor into the axillae of castrated mice. Vaginal smears in the host mice taken daily over a period of ten days all proved negative.

Histologic examination of the transplants showed degeneration of the tumor cells. The degenerated tumor cells have a striking resemblance to the excessively foamy, large lutein cells.

DISCUSSION

Although the biologically active tumors produced in mice after irradiation present variations in cellular differentiation and intensity of luteinization, their origin appears identical. The determination of the source of these neoplasms is dependent upon the interpretation of the earliest changes noted after irradiation. Our studies have led us to conclusions which in some respects differ from those of other authors. We believe that the granulosa cells within the follicles do not persist long after irradiation and do not proliferate to give rise to tumors. They appear to degenerate in the wake of ovum destruction. With the elimination of these structures there remains only interfollicular parenchyma together with persisting and proliferating theca interna cells. The term parenchyma is applied to the interfollicular tissue to indicate its functional potencies. The first evidence of growth is signaled by the simultaneous proliferation and luteinization of the theca interna and parenchymal cells. Thus a hyperplastic substrate or groundwork is established upon which neoplasia may appear many months later. So far as we have been able to determine, proliferation and luteinization progress together. We did not observe a primary proliferation and secondary luteinization of the newly formed cells.

It is generally accepted that luteinization is an effect of stimulation from the anterior lobe of the hypophysis. It must be recalled that the

entire mouse was exposed to the roentgen rays. Regaud and Lacassagne[15] have shown that the hypophysis is resistant to x-rays. Whether or not the hypophysis is actually stimulated by irradiation is a matter of conjecture. Further investigations in this direction are being pursued.

It is concluded that biologically active luteinized tumors produced in the ovaries of irradiated mice are derived from the undifferentiated parenchymal cell of the ovary. The granulosa cells of the Graafian follicle play no role in the genesis of the tumors. The theca interna cells, however, participate with the parenchymal cell in the early post-radiation proliferation and luteinization.

The feminizing neoplasms of the human ovary resemble those produced in mice. They include the granulosa cell tumor and its more luteinized variant—the "folliculome lipidique" of Lecène and the theca cell tumor. We do not consider the so-called luteoma a distinct entity. It is our impression that the reported cases of luteoma may fall into one of several categories, namely, granulosa cell tumor with marked luteinization, adrenal rest tumor or metastatic carcinoma.

Robert Meyer[16] suggested that granulosa cell tumors were derived from persisting embryonic "granulosa cell rests" which proliferated in later life under the influence of some unusual stimulus. He based this theory upon the isolated finding in the ovary of a forty-five-year-old woman of small masses of cells resembling those of the granulosa. Similar nests of cells were seen in the ovarian medulla of full-term fetuses and young infants. The great difficulty in finding such embryonic rests in normal ovaries of adult women militates against the "granulosaballen" concept of Meyer. Furthermore, we have experienced the ease with which a tangential section of a normal follicle may be mistaken for such "rests." Robinson's[21] contention that the tumor arises from mature granulosa cells of the Graafian follicle has not attracted many adherents. The granulosa is a well-differentiated tissue, satellite to the ovum and possibly dependent on it for its existence. Finally, granulosa cell tumors may occur years after the menopause, when follicular activity has long since ceased.

Our studies[12] of a number of theca cell tumors of the ovary reported previously suggest that genetically the theca and granulosa cells have a common origin. This is in accord with Fischel's concept that it is not the surface epithelium but the premature mesenchyme of the ovary which gives rise to the parenchyma, theca and granulosa cells. Theca cell tumors may show a variegated cell structure including fibromatous tissue, interlacing bundles of plump, epithelioid cells containing doubly refractile fat and rounded, more luteinized cells. These variations are attributable to the same differences in cell differentiation and physiologic response which obtain in the mouse tumors. Tumors containing both theca and granulosa elements have been described.[14] Such tumors merely illustrate a bilateral development from a common stem cell.

A group of cases are now being studied which reveal that in certain endocrinologic disturbances, especially those included in the broad term

of ovarian-adrenal syndrome, the human ovary may show proliferation and partial differentiation of the parenchyma with patchy luteinization.

SUMMARY

X-ray irradiation of mice at puberty results in the production of two types of ovarian tumors: tubular adenomas derived from the surface epithelium and parenchymal lutein tumors.

The parenchymal lutein tumors alone exhibit hormonal activity expressed in proliferative changes in the endometrium and vaginal mucosa.

Histologically, these tumors are composed of granulosa and theca cells with varying degrees of luteinization. They are entirely comparable to the granulosa cell tumor and its excessively luteinized variant, the Lecène tumor, and the theca cell tumor of the human ovary.

The luteinized ovarian tumors in mice are derived from the undifferentiated parenchyma. While the theca interna cells participate in the early proliferation and luteinization, the mature granulosa cells play no role in the genesis of these neoplasms.

The histogenesis of the analogous human tumors may well be identical.

REFERENCES

(1) *Brambell, F. W. R., Parkes, A. S., and Fielding, U.:* Proc. Roy. Soc., Ser. B. **101:** 29, 1927. (2) *Brambell, F. W. R., Parkes, A. S.:* Ibid. **101:** 316, 1927. (3) *Brambell, F. W. R., Parkes, A. S., and Fielding, U.:* Ibid. **101:** 95, 1927. (4) *Brambell, F. W. R., Fielding, U., and Parkes, A. S.:* Ibid. **102:** 385, 1928. (5) *Brambell, F. W. R., and Parkes, A. S.:* Ibid. **105:** 63, 1929. (6) *Butterworth, J. S.:* Am. J. Cancer **31:** 85, 1937. (7) *Cosacesco, A. S., Georgesco, M., and Denischiatu, G. T.:* Presse méd. **39:** 1264, 1931. (8) *Furth, J., and Furth, O. B.:* Am. J. Cancer **28:** 54, 1936. (9) *Furth, J., and Butterworth, J. S.:* Am. J. Cancer **28:** 66, 1936. (10) *Geist, S. H.:* Am. J. Obst. & Gynec. **30:** 480, 1935. (11) *Idem:* Ibid. **30:** 650, 1935. (12) *Geist, S. H., and Gaines, J. A.:* Ibid. **35:** 39, 1938. (13) *Glynn, E.:* J. Obst. & Gynaec. Brit. Emp. **28:** 23, 1921. (14) *Greenhill, J. P., and Greenblatt, R. B.:* Am. J. Obst. & Gynec. **36:** 684, 1938. (15) *Regaud, Cl., and Lacassagne, A.:* Handbuch d. ges. Strahlenheilkunde, ed. by Paul Lazarus, ed. 2, **1:** Munich, 1928. (16) *Meyer, R.:* Am. J. Obst. & Gynec. **22:** 697, 1931. (17) *McIntyre, D.:* J. Obst. & Gynaec. Brit. Emp. **38:** 302, 1931. (18) *Novak, E., and Brawner, J. N.:* Am. J. Obst. & Gynec. **28:** 637, 1934. (19) *Parkes, A. S.:* Proc. Roy. Soc., Ser. B. **101:** 71, 1927. (20) *Idem:* Ibid. **102:** 51, 1928. (21) *Robinson, M. R.:* Surg. Gynec. Obst. **51:** 321, 1930. (22) *Rottino, A.:* Proc. N. Y. Path. Soc. **19:** 19, 1937-38. (23) *Traut, H. F., and Butterworth, J. S.:* Am. J. Obst. & Gynec. **34:** 987, 1937. (24) *Wells, S. H., and Romano, S. A.:* Ibid. **29:** 845, 1935. (25) *Wolfe, S.:* Ibid. **13:** 575, 1927.

A STUDY OF THE RETICULUM AND OF LUTEINIZATION IN GRANULOSA AND THECA CELL TUMORS OF THE OVARY*

HERBERT F. TRAUT, M.D., ALBERTA KUDER, M.A., AND
J. F. CADDEN, M.A., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, Cornell University Medical College and New York Hospital)

GRANULOSA cell tumors, which were first described by von Kahlden in 1895, now occupy a well-established place in the pathology of the ovary. The folliculomatous, cylindromatous and undifferentiated variations of the granulosa tumor are generally well recognized. However, the lipoid changes or so-called luteinization which any form of the tumor may undergo are not so well known or so well understood, not only because they are much less frequently seen, but also because they have not been so intensively studied.

Our interest in the process of luteinization in these tumors arose, in part, because we encountered a large, nearly completely luteinized human tumor, but more particularly because in a previously reported study of granulosa cell tumors which were artificially produced in the ovary of the mouse by means of x-ray radiation, the luteinized tumors were found to be very common. In a series of 52 mouse tumors, luteinized forms were encountered with such frequency (42 per cent) that it was possible to study the different stages of the process in detail. Inasmuch as human luteinized tumors are difficult to obtain, the mouse tumors furnish a material which permits the filling of gaps that otherwise would remain open. The purpose of this report is to convey some of the information that has accumulated to date.

At the outset it may be well to state that so-called luteinization of the human granulosa cell neoplasms is not so uncommon as many have thought. This conclusion is based upon a careful survey of the entire literature upon the subject of granulosa tumors, as well as that of "luteomas" and those tumors of the ovary which have been classified as hypernephromas. Of completely luteinized human tumors, or so-called "luteomas," 9 instances have been found which may be accepted with little or no question (Table I). Seventeen granulosa tumors have been reported showing lutein changes to a major degree (Table II). Minor luteinization is of comparative frequence, consequently no attempt is made toward a complete survey. A considerable number of tumors, which have been reported as luteomas, cannot be accepted as properly belonging to this category either because they can be identified as belonging to some other group or because insufficient data are available to classify them definitely.

*Presented, by invitation, at the Sixty-Fourth Annual Meeting of the American Gynecological Society, White Sulphur Springs, W. Va., May 22 to 24, 1939.

TABLE I. LUTEOMAS

1908	Gardner and McCleary
1913	Massabuau
1918	Gordon } Accepted upon Turnbull and Leith
1920	Gordon } Murray's careful analysis
1927	Wolfe, S. A.
1931	Cosacesco, Draganesco, Georgesco, Dinischiotu
1931	Habbe, K., Case 18
1937	Torres, P. R.
1938	Viana, O.

TABLE II. GRANULOSA TUMORS LUTEINIZED TO A MAJOR DEGREE

1899	Gottschalk, S.
1902	Michelazzi
1910	Christian, E.
1922	Aschner, B.
1927	Lecène
1928	Cattaneo, L.
1933	Plate, W. P.
1934	Benda and Kraus
1934	Novak, E.
1935	Cutler, O. L.
1935	Decoulx, BéDrine and Bastien
1935	Wills and Romano
1936	Vayssiere, Mosinger, etc.
1937	Bourg & Roemans
1938	Delarue and Isidor
1938	Thomson and Stabler
1939	Traut, Kuder and Cadden

It is interesting to note that during the twenty-eight years following the report of the first luteinized tumor by Gottschalk in 1899, only 5 tumors showing lutein changes were reported; whereas, since Lecène again brought this type of tumor to the attention of the profession in 1927, 12 examples have been noted, and of these, 10 have appeared in the past six years. This would seem to promise more frequent mention and greater familiarity with this type of tumor in the future.

What is the nature of the metamorphosis which the granulosa cell undergoes in its transformation into a lutein cell? We know that in the normal Graafian follicle there are marked changes in the granulosa cells which may be specifically described as: (1) an increase in size of the cell from 15 μ to about 45 μ in diameter; (2) an alteration of the mitochondria from long rods (Levi) or intricate networks (Chydenius) to short fragments which finally disappear (Horrenberger); (3) an enlargement of the Golgi network, which is followed by a process of involution, in which the net assumes a position more remote from the nucleus (Riquier); (4) whereas mitoses are frequent in granulosa cells, they are seldom observed in lutein cells; (5) and finally, there is a marked change in the lipoid constituents, such that during the phase of hormonal activity of the cell there is an increase in phospholipid and cholesterol content, both of which are subsequently replaced by cholesterol esters and fats (Table III).

The work of Bloor, Okey and Corner, as well as that of Boyd and Elden, correlating the relationships between physiologic activity, on

the one hand, and the lipoid content of the lutein cells of the sow's ovary, on the other, is most significant (Figs. 1 and 2). These workers conclude that the phospholipid content of the lutein cell as demonstrated by histochemical tests is an index to its potential activity, and the ratio of phospholipid to cholesterol is an indication of actual or resultant activity emanating from metabolism within the cell. The fact that these values vary directly with the output of hormones (Table V) is most significant, particularly when it is remembered that estrone and progesterone are sterol derivatives.

Inasmuch as the term luteinization has come to mean such specific and definite changes in the normal granulosa cell, it may be instructive to examine the neoplastic cells of similar origin to determine whether

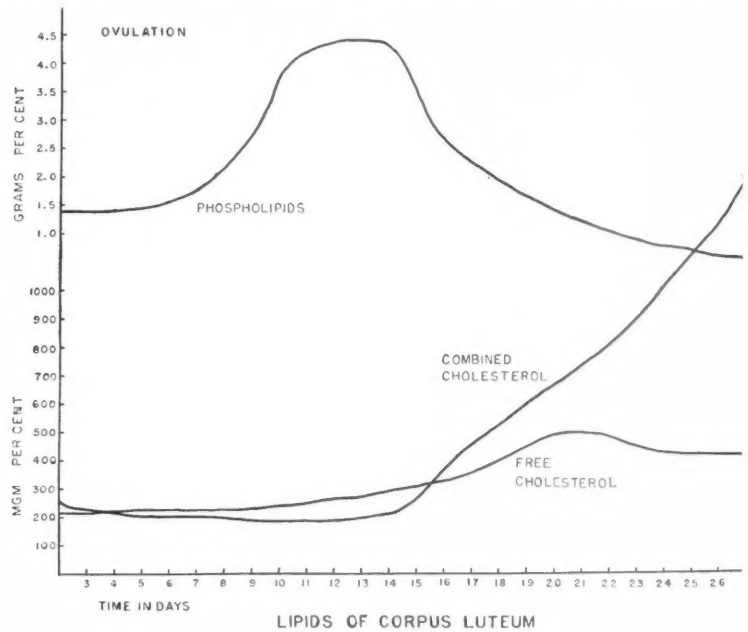

Fig. 1.—Graph showing the concentration of phospholipids, combined cholesterol, and free cholesterol in the corpus luteum of the sow's ovary in the various days after ovulation. (Bloor, Okey and Corner.)

TABLE III. CYTOLOGIC CRITERIA OF LUTEINIZATION AND FATTY DEGENERATION OF THECA AND GRANULOSA CELLS

		LUTEINIZATION	FATTY DEGENERATION
Macroscopic:	Yellow (Carotin) Pigmentation	Marked	Slight or absent
Microscopic	Hypertrophy	15 to 45 Micra	Irregular
	Golgi body	Enlargement and fragmentation	Displaced to one pole or absent
	Mitochondria	Shortening and disappearance of rods	None present
	Nucleus	Normal	Various stages of chromolysis
Chemical	Lipoids	1. Phospholipids 2. Free cholesterol 3. Combined cholesterol	1. Neutral and acid fats 2. Esters 3. Soaps

or not the same or similar changes take place, and to differentiate between luteinization, on the one hand, and fatty degeneration, on the other.

Early in our study of the mouse tumors it was noted that, with few exceptions, lutein changes occurred in the older neoplasms, that is, in

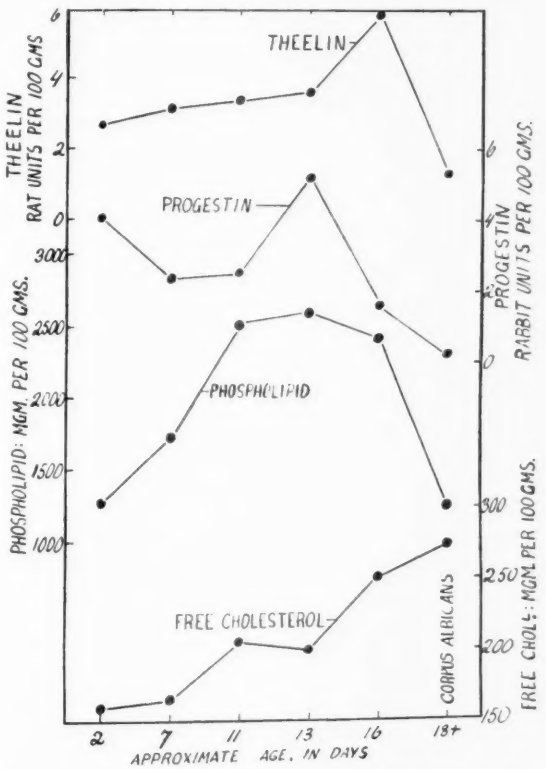

Fig. 2.—Graph showing the relationship of phospholipids and free cholesterol to the theelin and progestin in the corpus luteum of the sow's ovary in the various days after ovulation. (Boyd and Elden.)

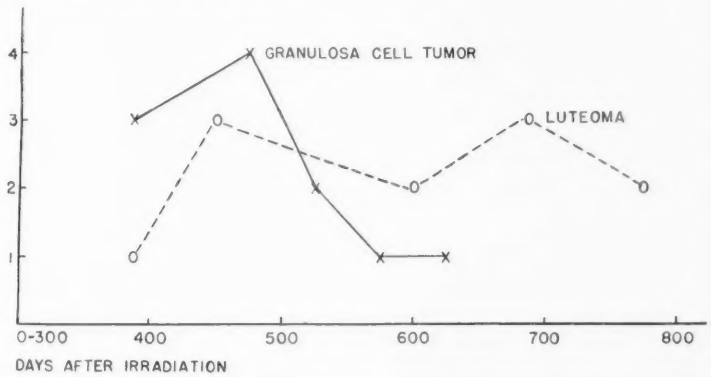

Fig. 3.—Showing the age incidence of granulosa cell tumors in the mouse's ovary as compared to the incidence of lutein tumors. It would seem that in general the lutein tumors are definitely of greater age than are the granulosa tumors.

those mice which had survived longest after the radiation of the body (Fig. 3). This has suggested the possibility that lutein changes may be a function of the maturity of the cell rather than a response to hormonal influence from the anterior hypophysis, as is indicated by the currently accepted concept of the cause of luteinization. In addition to this observation, one of the mice had bilateral ovarian tumors,

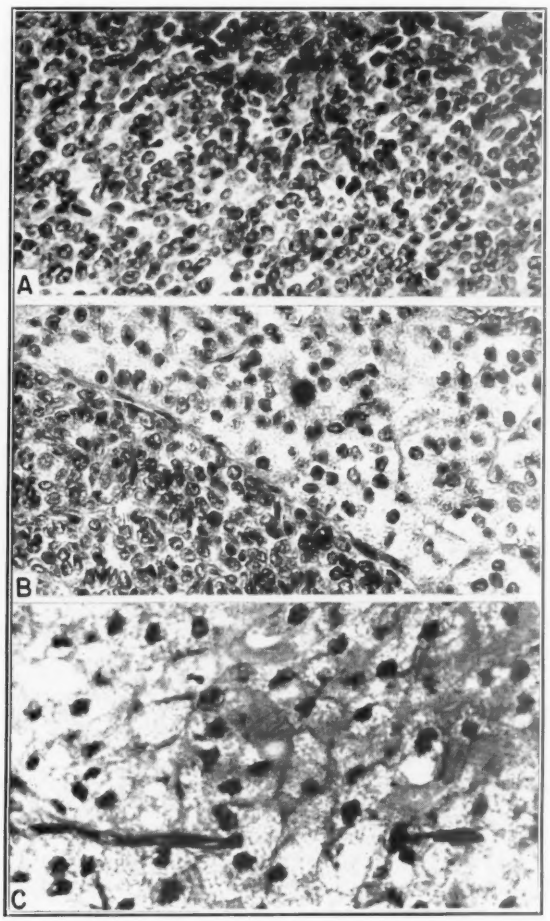

Fig. 4, *A*, *B*, *C*.—Hematoxylin and eosin stain. Zenker-formol fixation. (×520.) *A*, A section from the granulosa tumor of the mouse's ovary, showing little or no differentiation and no attempt at luteinization. *B*, A section from the granulosa cell tumor of the mouse's ovary undergoing a process of luteinization. *C*, A section from the granulosa tumor of the mouse's ovary, showing almost complete luteinization.

one of which was completely "luteinized," while the other was distinctly granulosal in character. The possible role of maturity in the production of the so-called luteinization of the granulosa tumors also suggests strongly that the accumulation of fat may be primarily a matter of senescence or degeneration, and therefore not strictly analogous to luteinization as we understand it in the normal Graafian follicle (Fig. 4, *A*, *B*, *C*).

Since we are interested primarily in gaining knowledge which may be of value to the human patient, most emphasis has been placed upon the study of the human tumors, using the mouse tumors only as a source material to which we could refer for corroborative or negative evidence. This communication is based on a study of five human tumors, one of which shows marked luteinization, the second lutein changes to a lesser degree, while two are typical, well-differentiated

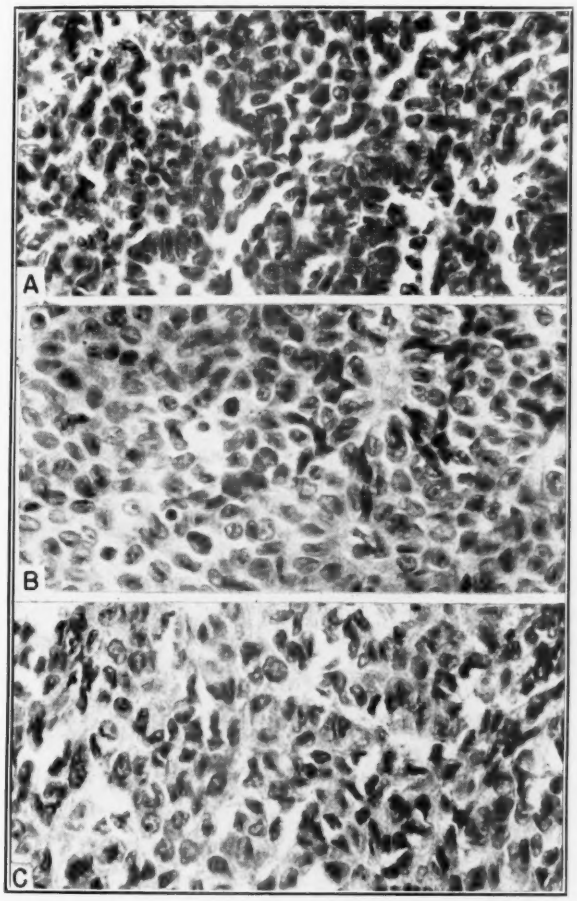

Fig. 5, *A, B, C.*—Human granulosa cell tumors. Zenker-formol fixation. (×520.) *A*, A section from Tumor 1, showing a portion of the cylindromatous type of tumor, with very little differentiation. *B*, A section from Tumor 2 showing the Call and Exner bodies and an occasional lutein cell. *C*, A section from Tumor 3 showing beginning lutein changes.

granulosa tumors, and the fifth is a tumor which may be characterized as being borderline between the granulosa and theca cell varieties (Fig. 5, *A, B, C, D, E, F*).

Because our material had been fixed in formalin, hormone assay could not be carried out, and we were therefore dependent upon (1) the endometrial response; (2) the chemical analysis; and (3) the stain-

ing reactions of the cells in the evaluations of their biologic activity. For similar reasons we have not been able to study the more minute details of cellular architecture, such as mitochondria and Golgi networks, for they rapidly disintegrate with ordinary fixation; therefore, evaluation of these must be reserved for a later report.

In recent years, the use of stains in their application to the study of reticulum and of lipoid substances has been greatly advanced. To

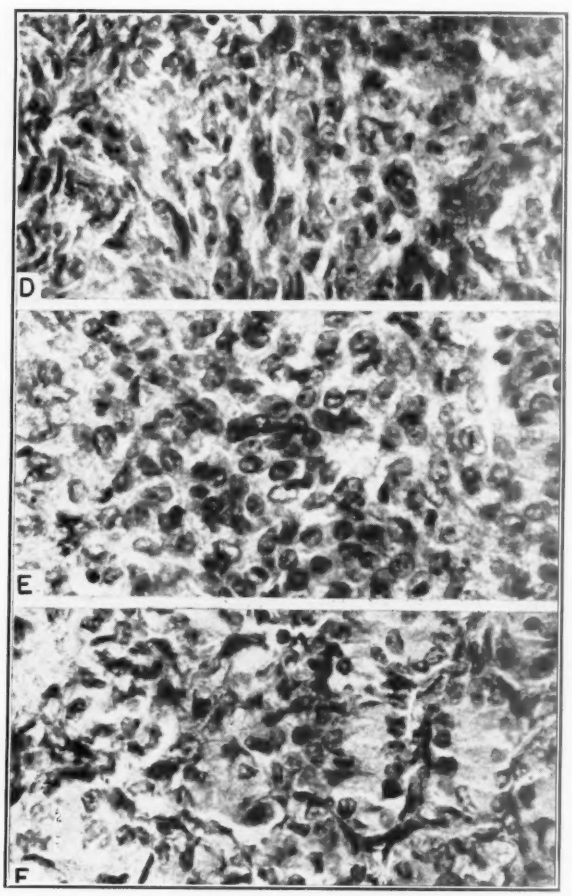

Fig. 5, *D, E, F.*—Human granulosa cell tumors. Zenker-formol fixation. (×520.) *D,* A section from Tumor 4 of the theca-granulosa type, showing a portion of the tumor which is predominantly thecal in character. *E,* Another portion of Tumor 4, showing granulosa cells predominating, with commencing luteinization. *F,* A section from Tumor 5, which is a granulosa cell tumor that is almost completely luteinized, showing characteristic lutein cells.

demonstrate the reticulum, we have used the Foot silver stain. In the visualization of lipoid and fatty substances, the osmic acid-Sudan technique of Hoerr and Romeis has made possible the histologic demonstration of the intracellular lipid and lipoid content. To the latter we shall return, but first let us consider the reticulum (Fig. 6, *A, B, C, D, E*).

Since Loeffler and Priesel first described the theca cell neoplasms, pathologists have striven to decide whether the tumor should be considered as a separate entity or simply another variety of granulosa cell tumor. Recently there has been an increasing tendency to consider them as very closely related, some observers going so far as to say that the theca cell tumors cannot be established as a separate group

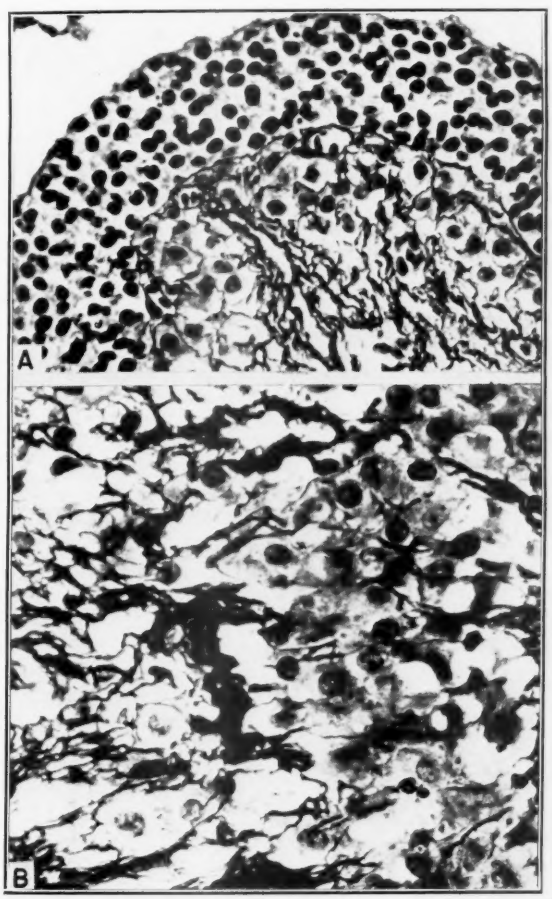

Fig. 6, *A*, *B*.—Stained with Foot's silver stain. (×520.) *A*, A section from the margin of the normal, recently ruptured Graafian follicle, showing the granulosal layer, distinctly demarcated from the theca by the reticulum. Each thecal cell is distinctly surrounded by the net of reticulum. *B*, A section from the normal corpus luteum, showing the relationship of the reticulum to the theca-lutein and granulosa lutein cell. The lower margin shows a few of the theca-lutein cells enmeshed in dense reticular structures. The middle portion shows the granulosa lutein cells with only slight filaments of reticulum penetrating this layer.

of tumors, basing their opinion upon the discovery of tumors made up of both elements. This study, with the use of the silver stain, tends to strengthen the latter view.

By referring to Fig. 6, *A*, representing an early stage in the development of the corpus luteum, the intimate relationship of the reticular envelope to each individual theca cell is clearly shown. In fact, the

line of demarcation between the theca and granulosa cells when the silver stain is used is so sharply drawn that it is impossible to confuse the two types of cells. In the mature corpus luteum, the same relationship maintains to a lesser degree (Fig. 6, *B*) in that the theca lutein cells are always surrounded by reticulum, the strands of which grow more and more dense, whereas the granulosa lutein cells are involved in a gradually increasing network of the finest terminal strands.

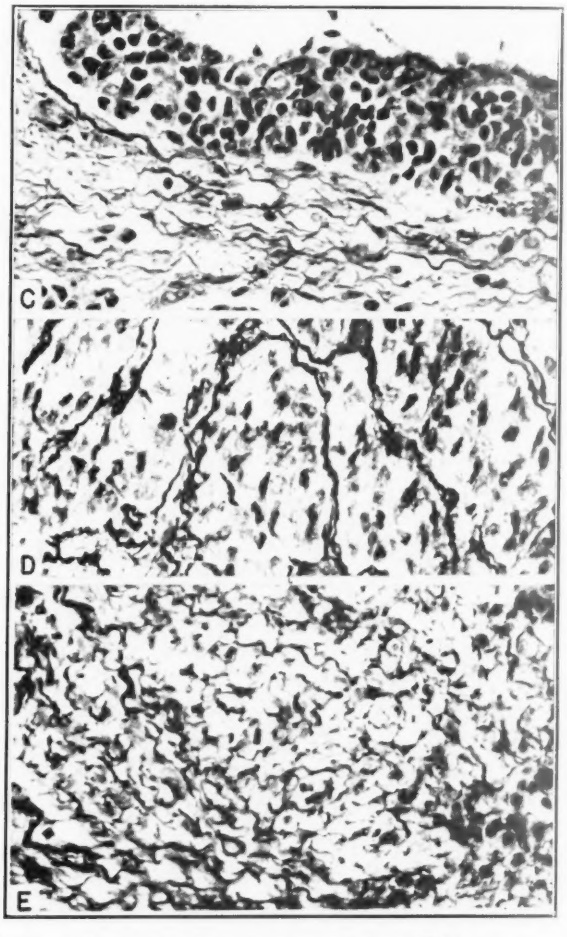

Fig. 6, *C*, *D*, *E*.—Stained with Foot's silver stain. (×520.) *C*, A section from the folliculomatous type of granulosa cell tumor. The granulosa cell layer is very distinct and separated from the lamina propria composed of reticulum in which are enmeshed theca-lutein cells. *D*, A section from a luteinized granulosa cell tumor showing islands of lutein cells separated by fine network of reticulum. Individual lutein cells are quite free of any reticular involvement. *E*, A section from the theca-granulosa cell tumor showing the theca cells enmeshed individually and a very extensive reticular framework.

However, the granulosa lutein cells are never so completely enmeshed as is the case with the theca cells.

This relationship of reticulum to the two types of cells is very helpful in studying tumors of theca and granulosa origin, for one can

thereby differentiate between the two types of cells with a very satisfactory degree of certainty (Fig. 6, *C, D, E*).

Furthermore, the use of this criterion convinces one that in the well-differentiated or folliculomatous types of granulosa cell tumors, as well as in the more undifferentiated types, we actually have representatives of both cellular layers of the Graafian follicle. In other words, many so-called granulosa cell tumors contain considerable quantities of thecal elements. It seems probable that further study will reveal that we should not draw too close a line of demarcation between theca cell tumors, on the one hand, and granulosa cell tumors, on the other. Their physiologic activities are identical, and as we know more about their cytologic relationships, it seems more than likely that we shall conclude that every tumor of this general category contains elements composed of representatives of the two varieties of cell. We have come to the conclusion, tentatively, that this is true, basing our opinion upon the human material thus far examined. However, a more exhaustive study must be made upon many tumors before a definitive conclusion can be reached. This work is already under way in our laboratory upon 50 granulosa tumors collected from a number of hospitals in New York City.

We turn now to a consideration of the lipid and fatty changes as found in the human tumors. As a result of the chemical studies of Bloor, Okey and Corner, as well as those of Boyd and Elden, we may assume that in the sow's ovary, at least, the percentage content of phospholipid varies markedly with the activity of the gland, and in direct proportion to its hormonal output. These workers have shown that the phospholipid content of the cells is from two to three times as high during pre-estrus and pregnancy as during periods of development or regression of the gland. Free cholesterol also increases up to and including the same periods, but to a much smaller degree. On the other hand, cholesterol esters vary inversely with the activity of the organ. Therefore, we may say that a high phospholipid content of lutein tissue is a characteristic of physiologic activity. If this concept is correct, it is possible to measure the physiologic activity of a tissue without resort to a direct analysis of the hormonal output. Such an analysis may be done by determining the phospholipid, free cholesterol, and the cholesterolester content in the chemical laboratory. Another means of evaluating the lipid potentialities of a tissue is by use of the Hoerr-Romeis lipid staining technique (Table IV). This procedure has the advantage over chemical analysis of enabling one to see just what cells or what portions of the tissue are active, inactive, or degenerate.

TABLE IV. HOERR-ROMEIS TECHNIQUE FOR STAINING LIPINS

1. Fixation in Zenker-formol solution, 24 hours
2. Mordant in 3 per cent potassium dichromate solution, 2 days
3. 2 per cent osmic acid, 6 days
4. Embedding in gelatin
5. Frozen sectioning
6. Stain with Romeis' sudan III solution, 12 to 16 hours

By this treatment the phospholipid substances stain a faint rose pink, the free cholesterol takes a yellow amber color, and the esters, neutral and acid fats stain black (Fig. 7, *A*, *B*, *C*, *D*, *E*).

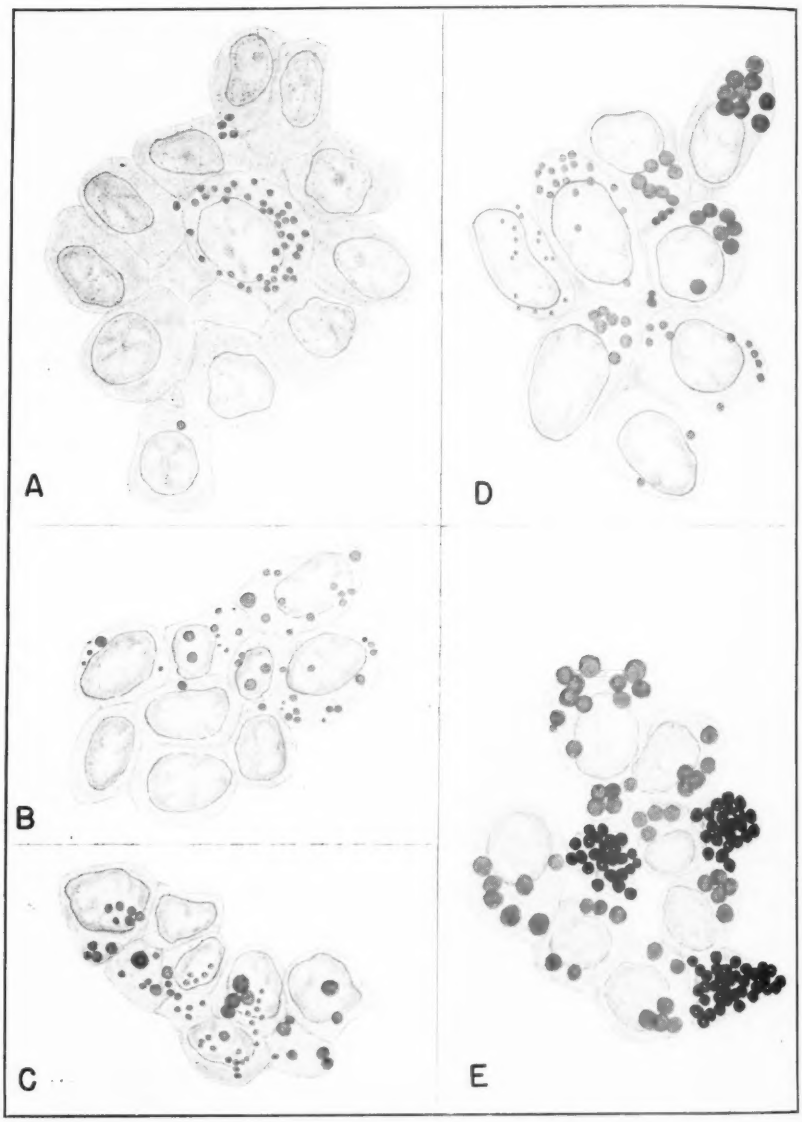

Fig. 7.—Camera-lucida drawings of representative sections from each of the five human tumors included in this study, stained by the Hoerr-Romeis technique to demonstrate phospholipids, fats and esters. *A*, A section from Tumor 1, showing small quantities of phospholipids (pale staining), in minute droplets. *B*, A section from Tumor 2, showing a greater concentration of phospholipid droplets which are indicated in the very pale gray as well as darker staining, cholesterol or cholesterol esters. *C*, A section from Tumor 3, showing some phospholipid (pale), with considerable representation of cholesterol droplets (dark), and some very dark-staining osmic reaction (black). *D*, A section from the theca-granulosa tumor, showing very considerable droplets of phospholipids, cholesterol and the more saturated fats and fatty acids. *E*, From the luteinized granulosa cell tumor, showing almost no phospholipids, a moderate amount of cholesterol, large quantities of cholesterol esters, fatty acids, neutral fats, and so forth.

Using the chemical and histologic methods of study upon the 5 human tumors, we find the following relationships existing between the lipoid content and the staining reactions, as compared to the clinical evidence of hormonal activity (Table V).

CASE 1.—A typical granulosa cell tumor of the cylindromatous type, measuring 15 by 8 by 7 cm., produced a marked hyperplasia of the endometrium in a woman three years beyond the menopause.

It contained 350* mg. per cent phospholipid, 580 mg. per cent free cholesterol, and 990 mg. per cent total cholesterol. The total fat content was 1070 mg. per cent. The fat stain reactions were sudan ++++ and osmic acid +.

TABLE V. SHOWING THE CONSOLIDATED RESULTS OF THE STUDY OF FIVE HUMAN TUMORS

TYPE OF TUMOR	ENDOMETRIAL HYPERPLASIA	SUDAN III REACTION	OSMIC ACID REACTION	PHOSPHOLIPID MG. %	FREE CHOLESTEROL MG. %	TOTAL CHOLESTEROL MG. %	TOTAL FAT MG. %
1. Granulosa	++++	++++	+	350	580	990	1,070
2. Granulosa	++++	++++	+	1,620	830	800	1,870
3. Granulosa	++	++	+++	310	890	1,120	3,775
4. Theca granulosa	++++	+++	++	520	370	710	2,822
5. Luteinized granulosa		+	++++	170	880	1,230	4,130

CASE 2.—A folliculomatous type of granulosa cell tumor measuring 2 by 3 by 5 cm., which also produced a marked hyperplasia of the endometrium in a woman of 40 years, who had had excessive metrorrhagia at four-month intervals for two and a half years.

This tumor contained 1,620 mg. per cent phospholipid, 830 mg. per cent free cholesterol, and 800 mg. per cent total cholesterol. The total fat content was 1,870 mg. per cent. The fat stains showed sudan ++++ and osmic acid +.

CASE 3.—A well-differentiated cylindromatous granulosa cell tumor, measuring 14 by 15 by 8 cm., produced a moderate hyperplasia of the endometrium in a 43-year-old woman who had had amenorrhea for a period of eighteen months, followed by excessive uterine bleeding.

The chemical analysis gave the lipoid relationships as phospholipid 310 mg. per cent, free cholesterol 890 mg. per cent, and total cholesterol 1,120 mg. per cent. The total fat content was 3,775 mg. per cent. The fat stains showed sudan ++ and osmic acid +++.

CASE 4.—A solid, theca granulosa cell type of tumor, measuring 8 by 7 by 4½ cm., producing a marked hyperplasia of the endometrium. The patient was 29 years of age and had experienced amenorrhea for three months, followed by scanty but continuous uterine bleeding.

Chemical analysis showed phospholipids 520 mg. per cent, free cholesterol 370 mg. per cent, and total cholesterol 710 mg. per cent. Total fat content was 2822 mg. per cent. The Hoerr-Romeis stain indicated sudan +++ and osmic reaction ++.

CASE 5.—A very marked luteinized granulosa cell tumor of cylindromatous type, measuring 21 by 17 by 11 cm., and could not be evaluated as to its hormone output because the uterus had been removed eighteen years previously.

The chemical analysis showed phospholipid content 170 mg. per cent, free cholesterol 880 mg. per cent, and total cholesterol 1,230 mg. per cent. The total fat content was 4,130 mg. per cent. The Hoerr-Romeis stain showed only sudan + reaction, while the osmic acid reaction was ++++.

*All weights are based on dry weight of tumor.

From the data presented, the Sudan III reaction indicating the presence of phospholipids in the cells may be said to parallel the phospholipid content of the tumors as determined by chemical analysis. The same statement is true of the end-products of lipoid metabolism, that is, the content of neutral fats, fatty acids, and esters is correspondingly indicated by the osmic acid reaction.

From a comparative study of these hormonally active tumors, using the chemical evaluation of the lipid content as one factor and the response to fat stains as another, certain conclusions can be drawn. It is at once apparent that, with the exception of Case 2, the phospholipid content of these tumors is small as compared with that of the normal corpus luteum, where values range from 800 to 2,700 mg. per cent. On the other hand, the free cholesterol values are much higher than in the normal corpus luteum. A completely satisfactory explanation of the significance of the low phospholipid-cholesterol ratio is not apparent, however; in spite of the low ratio, the tumors achieve an endometrial reaction which is more marked in its extent than is seen as a result of normal Graafian follicle effect which must be accounted for by the greater cell mass of the tumors and the fact that they produce their hormonal influence over much longer periods of time.

It also seems obvious that in a general way the phospholipid and free cholesterol content is somewhat parallel to hormonal activity, although hormone assays will need to be done on a similar group of tumors before this conclusion can be accepted without reservation.

In contrast to the corpus luteum, where most of the cells develop at about the same rate, and there is only moderate difference in the degree of maturity, in the granulosa tumor undergoing lipoid change there are the widest variations between foci of recent growth and others of marked maturity and even senescence. Parts of such a tumor, therefore, show a predominance of the phospholipid phase of metabolism, whereas others are rich in neutral and acid fats. The first, or phospholipid phase, is characteristic of hormonal potentialities and the latter, impotent, representing the end stages of the process of lipoid metabolism. The tumor, therefore, is composed of many areas with varying degrees of biologic activity and the effect of the neoplasm upon the body is a composite of the whole. This concept indicates clearly the greater difficulties and complexities encountered in the study of the neoplasm as compared with those attending an evaluation of the normal tissues.

It would seem, as far as one may judge at the present time, that the granulosa cell tumors may be said to undergo luteinization much as do the normal cells of the Graafian follicle in the sense that the lipoid metabolism of both is similar. Whether the transformations of mitochondria and the Golgi bodies, which are thought to be the chief repositories of the lipid elements, are analogous remains for further study to determine.

The granulosa cell neoplasm, similar to tumors in general and in contrast to the ovarian follicle or corpus luteum, is subject to accidental complications of its vascular supply by virtue of the fact that

it is a tumor. In rapidly growing portions of the tumor, the blood supply sometimes becomes inadequate. Such a state is followed by the ischemic necrosis and cyst formation, which are very common findings in most granulosa tumors of good size. Such an accident must inevitably be associated with marked fluctuation in the hormone output by the tumor mass.

These factors in the life history of the granulosa cells elucidate why some granulosa cell tumors are relatively asymptomatic, from the clinical point of view. It also explains why many of the so-called luteomas have shown little or nothing in the way of hormonal activity at the time of observation. For example, amenorrhea associated with granulosa cell tumors is of two kinds, first, that which occurs during the period of active growth of many cells, producing a high titer of estrone and hence, hyperplasia of the endometrium; and second, that due to luteinization of the tumor. Metrorrhagia, on the other hand, is probably present only when there is a drop in estrone titer which presumably follows maturation of the granulosa cells or ischemic necrosis of portions of the tumor.

SUMMARY

1. In the Graafian follicle and corpus luteum, as well as in tumors containing theca and granulosa cells, the relationship of the reticulum furnishes a means of identifying the two types of cells. The theca cells are always individually surrounded by this connective tissue element, whereas granulosa cells and lutein cells are enclosed not at all, or as groups of cells.

2. Granulosa and theca cell tumors are not only closely related, but in all probability, most human granulosa cell tumors contain varying proportions of both types of cells.

3. These tumors undergo luteinization in the same manner as does the Graafian follicle. The cause of luteinization is not known, excepting that it is found in the older tumors of the mouse's ovary and may be therefore an expression of age or maturity.

4. The phospholipid content of the tumors is low per unit of weight, as compared with that of the corpus luteum. This may, in part, be due to the greater connective tissue content and areas of degeneration.

5. The life cycle of the granulosa cells, together with the fact that the tumor composed of them contains foci which differ widely in degrees of maturity, explains some of the clinical phenomena observed in patients harboring this type of growth.

6. Luteinization of granulosa cell tumors in small or moderate degree is common. Seventeen instances reported in the literature have been found where the major portion of the tumor had undergone lipoid change. Complete luteinization is rare and is usually found in small tumors.

7. If allowed to mature, one of three different terminations is thought to be the end of the life cycle of granulosa cell tumors: (a) luteinization followed by lipoid degeneration; (b) ischemic necrosis; and (c)

collagenous degeneration followed by fibrosis. In tumors composed chiefly of theca elements, collagenous degeneration and fibrosis are the usual sequelae to the luteinization phase.

Dr. J. Furth of the Department of Pathology, Cornell Medical College, has been most kind in permitting the use of many mouse tumors, as well as in giving friendly advice and criticism, for all of which our thanks are warmly given.

REFERENCES

(1) *Abrahamer, I.:* Zentralbl. f. allg. Path. u. path. Anat. **53:** 310, 1932. (2) *Albanese, A.:* Atti d. r. Accad. fisiocrit in Siena **4:** 729, 1929. (3) *Allen, E., and Creadick, R. N.:* Anat. Rec. **69:** 191, 1937. (4) *Arnold, W., Koerner, J., and Mathias, E.:* Virchow's Arch. f. path. Anat. **277:** 48, 1930. (5) *Aron, M.:* Compt. rend. Soc. de biol. **111:** 34, 1932. (6) *Aschner, B.:* Arch. f. Gynäk. **115:** 350, 1922. (7) *Asdell, S. A.:* Physiol. Rev. **8:** 313, 1928. (8) *Bachmann, R.:* Ztschr. f. mikr.-Anat. Forsch. **41:** 433, 1937. (9) *Benckiser, A.:* Arch. f. Gynäk. **23:** 350, 1884. (10) *Benda, R., and Kraus, E. J.:* Ibid. **157:** 400, 1934. (11) *Bingel, A.:* Deutsche med. Wchnschr. **50:** 330, 1924. (12) *Blau, A.:* Arch. f. Gynäk. **81:** 421, 1907. (13) *Bourg, R., and Rocmans, M.:* Bruxelles-méd. **17:** 1831, 1937. (14) *Brambell, F. W. R.:* Proc. Roy. Soc., London, s. B. **101:** 391, 1927. (15) *Bulgaru, M.:* Cluj. med. **8:** 85, 1927. (16) *Cattaneo, L.:* Ann. di ostet. e ginec. **50:** 483, 1928. (17) *Christian, E.:* Bull. et mém. Soc. Anat. de Paris **85:** 639, 1910. (18) *Corner, G. W.:* Anat. Rec. **13:** 109, 1917. (19) *Idem:* Am. J. Anat. **26:** 117, 1919. (20) *Corner, G. W., and Amsbaugh, A. E.:* Anat. Rec. **12:** 287, 1917. (21) *Cosacesco, Draganesco, Georgesco, and Dinischiotu:* Presse med. **39:** 1264, 1931. (22) *Cutler, O. L.:* Am. J. Obst. & Gynec. **30:** 131, 1935. (23) *Deanesly, R.:* Proc. Roy. Soc., London, s. B. **106:** 578, 1930. (24) *Idem:* Ibid. **107:** 60, 1930. (25) *Decoulx, Bédrine, and Bastien:* Bull. Soc. d'obst. et de gynéc. **24:** 458, 1935. (26) *Delarue, J., and Isidor, P.:* Bull. Assoc. franc. p. l'étude du cancer **27:** 429, 1938. (27) *Downes, W. A., and Knox, L. C.:* J. A. M. A. **82:** 1315, 1924. (28) *Dworzak, H.:* Zentralbl. f. Gynäk. **56:** 1033, 1932. (29) *Enfenger, H., and Bader, C. W.:* Arch. f. Gynäk. **124:** 483, 1925. (30) *Engle, E. T., and Smith, P. E.:* Anat. Rec. **43:** 239, 1929. (31) *Fenger, F.:* J. A. M. A. **62:** 1249, 1914. (32) *Flössner, O.:* Arch. f. Gynäk. **135:** 474, 1929. (33) *Fournier, M.:* Bull. Soc. d'obst. et de gynec. **12:** 421, 1923. (34) *Galesesco, P., and Bratiano, S.:* Compt. rend. Soc. de biol. **99:** 1460, 1928. (35) *Gallo, A. G., and Gallo, S.:* Bol. y trab. de la Soc. de cir. de Buenos Aires **20:** 77, 1936. (36) *Gardner, W. S., and McCleary, S.:* Surg. Gynec. Obst. **7:** 669, 1908. (37) *Geist, S. H.:* Am. J. Obst. & Gynec. **30:** 650, 1935. (38) *Geller, F. C.:* Ber. ü. d. ges. Gynäk. u. Geburtsh. **25:** 433, 1933. (39) *Glynn, E.:* J. Obst. & Gynaec., Brit. Emp. **28:** 23, 1921. (40) *Goldmann, J.:* Centralbl. f. allg. Path. u. path. Anat. **58:** 275, 1933. (41) *Goormaghtigh, N.:* Arch. de biol., Paris **37:** 46, 1927. (42) *Gordon, A. K.:* Brit. M. J. **1:** 133, 1920. (43) *Gottschalk, S.:* Arch. f. Gynäk. **59:** 676, 1899. (44) *Greenhill, J. P., and Greenblatt, R. W.:* Am. J. Obst. & Gynec. **36:** 684, 1938. (45) *Grouzdew, V.:* Arch. f. Gynäk. **70:** 445, 1903. (46) *Habbe, K.:* Zentralbl. f. Gynäk. **55:** 1088, 1931. (47) *Hammar, S.:* Acta obst. et gynec. Scandinav. **17:** 516, 1937. (48) *Haven, F. L.:* Am. J. Cancer **29:** 57, 1937. (49) *Hermstein, A.:* Arch. f. Gynäk. **124:** 739, 1925. (50) *Idem:* Zentralbl. f. Gynäk. **53:** 2258, 1929. (51) *Hochloff, A. W.:* Arch. f. Gynäk. **136:** 623, 1929. (52) *Hoerr, N. L.:* Anat. Rec. **66:** 149, 1936. (53) *Idem:* Ibid. **66:** 317, 1936. (54) *Horrenberger, R.:* Arch. d'anat. d'histol. et d'embryol. **8:** 128, 1928. (55) *Idem:* Compt. rend. Soc. de biol. **98:** 849, 1928. (56) *Idem:* Ibid. **98:** 851, 1928. (57) *Ishikawa, M.:* Jahresb. ü. d. ges. Gynäk. u. Geburtsh. **36:** 388, 1921. (58) *Jkeda, K.:* Ztschr. f. Geburtsh. u. Gynäk. **93:** 229, 1928. (59) *Kaufmann, C.:* Ibid. **91:** 668, 1927. (60) *Kaufmann, C., and Raeth, K.:* Arch. f. Gynäk. **130:** 128, 1927. (61) *Kermauner, F.:* Stoeckel, Handbuch der Gynäkologie **7:** München, 1932, J. F. Bergmann, p. 346. (62) *Kingsbury, B. F.:* Am. J. Anat. **15:** 345, 1914. (63) *Knox, R.:* Lancet **2:** 226, 1840. (64) *Long, J. A., and Evans, H. M.:* Mem. Univ. California, No. 6, 1922. (65) *Lustig, B., and Mandler, E.:* Biochem. Ztschr. **261:** 132, 1933. (66) *Morkovitch, M.:* Contribution a l'etude des tumeurs de l'ovaire a cellules luteiniques, These Montpellier, 1913. (67) *Masson, P.:* Tumeurs. Diagnostics Histologiques, Paris, 1923, A. Maloine et fils. (68) *McIntyre, D.:* J. Obst. & Gynaec. Brit. Emp. **38:** 302, 1931. (69) *Michelazzi, A.:* Riforma med. **3:** 470, 1902. (70) *Miller, J. W.:* Arch. f. Gynäk. **91:** 263, 1910. (71) *Motta, G.:* Zentralbl. f. Gynäk. **60:** 1547, 1936. (72) *Moulonguet, P.:* Arch. internat. de med. exper. **2:** 271, 1925. (73) *Idem:*

Compt. rend. Soc. de biol. **95:** 1323, 1926. (74) *Idem:* Ibid. **95:** 1392, 1926. (75) *Idem:* Ibid. **97:** 1652, 1928. (76) *Idem:* Les diagnostics anatomo-cliniques de B. Lecène. Appareil genital de la femme, Paris, 1932, Masson & Cie **2:** p. 308, 1932. (77) *Nizza, M.:* Boll. de Soc. piemontese di ostet. e ginec. **2:** 634, 1934. (78) *Novak, J., and Wallis, O.:* Arch. f. Gynäk. **164:** 543, 1937. (79) *Ossiakina, A. I.:* J. akush. i zhensk. bolïez. **40:** 228, 1929. (80) *Parhon, Dumitresco, and Nissipesco:* Compt. rend. Soc. de biol. **66:** 650, 1909. (81) *Peraus, A.:* Ibid. **119:** 771, 1935. (82) *Plate, W. P.:* Arch. f. Gynäk. **153:** 318, 1933. (83) *Policard, A. A., and Ferrand, M.:* Compt. rend. Soc. de biol. **122:** 200, 1936. (84) *Portes, Aschheim, and Robey:* Gynec. et obst. **37:** 100, 1938. (85) *Pratt, F. B.:* J. Obst. & Gynaec. Brit. Emp. **44:** 880, 1937. (86) *Preissecker, E.:* Zentralbl. f. Gynäk. **52:** 2740, 1928. (87) *Riquier, J. K.:* Arch. f. mikr. Anat. **75:** 772, 1910. (88) *Romeis, B.:* Ztschr. f. mikr.-anat. Forsch. **16:** 525, 1929. (89) *Idem:* Centralbl. f. allg. Path. u. path. Anat. **66:** 97, 1936. (90) *Salazar, A. L.:* Compt. rend. Soc. de biol. **124:** 1032, 1937. (91) *Santi, E.:* Ann. di ostet. e ginec. **27:** 1, 1905. (92) *Savage, S.:* Brit. M. J. **2:** 1032, 1909. (93) *Schaller and Pförringer:* Beitr. z. Geburtsh. u. Gynäk. **2:** 91, 1899. (94) *Simkins, C. S.:* Am. J. Anat. **51:** 465, 1932. (95) *Skowron, S., and Keller, T.:* Ztschr. f. Zellforsch. u. mikr. Anat. **21:** 425, 1934. (96) *Sobotta, J.:* Arch. f. mikr. Anat. **47:** 261, 1896. (97) *Solomons, B., and Gatenby, J. W. B.:* J. Obst. & Gynaec. Brit. Emp. **31:** 580, 1924. (98) *Steinforth, T.:* Ztschr. f. Geburtsh. u. Gynäk. **92:** 71, 1927. (99) *Stieve, H.:* Ztschr. f. mikr. anat. Forsch. **10:** 225, 1927. (100) *Thomson, J. G., and Stabler, F.:* J. Obst. & Gynaec. Brit. Emp. **45:** 769, 1938. (101) *Topchieva, O. J.:* J. akush. i zhensk. bolïez. **39:** 157, 1928. (102) *Idem:* Ibid. **40:** 221, 1939. (103) *Torres, P. R.:* Semana med. **1:** 1358, 1937. (104) *Traut, H. F., and Butterworth, J. S.:* Am. J. Obst. & Gynec. **34:** 987, 1937. (105) *Vayssiere, Mosinger, et al.:* Bull. Soc. gynec. et d'obst. **25:** 321, 1936. (106) *Viana, O.:* Atti Soc. ital. di ostet. e ginec. **34:** 522, 1938. (107) *Wallart, J.:* Arch. f. Gynäk. **135:** 485, 1929. (108) *Watrin, M.:* Arch. internat. de med. exper. **1:** 97, 1924. (109) *Idem:* Arch. internat. de med. exper. **1:** 209, 1924. (110) *Idem:* Ibid. **2:** 203, 1925. (111) *Westman, A.:* Acta obst. et gynec. Scandinav. **8:** 290, 1929. (112) *Wiczynski, T.:* Polska gaz. lek. **10:** 100, 1931. (113) *Wills, S. H., and Romano, S. A.:* Am. J. Obst. & Gynec. **29:** 845, 1935. (114) *Wolfe, S. A.:* Ibid. **13:** 575, 1927. (115) *Yosuda, M., and Bloor, W. R.:* J. Clin. Investigation **11:** 677, 1932.

DISCUSSION ON PAPERS BY DRS. GEIST, GAINES AND POLLACK, AND TRAUT, KUDER AND CADDEN

DR. NORMAN F. MILLER, Ann Arbor, Mich.—These contributions have been of great value in clearing away much of the haze which has surrounded the origin, life cycle, and the variable histologic picture of the granulosa cell group of tumors. These studies explain also the inconsistent clinical syndrome associated wtih such tumors in the human being. Finally on the basis of work here presented I am willing to accept a single stem or cellular precursor. Whether this be embryonic granulosa cell rests, as has been suggested by Meyer, or undifferentiated parenchymal cells as stressed by Geist, requires further study before a decision can be reached. There appears to be little doubt, however, that the granulosa cells of the Graafian follicles play no etiologic role.

By placing the granulosa, theca and so-called lutein tumors in a single group, a real step toward simplification in classification has been made. Since luteinization is merely a phase in the life cycle of these tumors and since both theca and granulosa cellular elements are found in varying proportions, the question of simplified nomenclature might be considered. Why not rename this group of tumors, simply yet significantly?

Since reading these papers I have toyed with the thought that here we may have a clue to the interesting behavior of 30 per cent of women under 40 years of age, castrated by means of radiation. In a follow-up study of approximately 360 noncancerous women between the ages of 35 and 50 treated by means of radiation, Kretzchmar and Brown in my clinic discovered that the so-called radiation menopause has been overemphasized. Thirty per cent of the women under 40 years of age, when treated with what was considered to be an adequate castration dose of either x-ray or radium, and in whom menstruation ceased permanently, did not develop any of the common subjective symptoms of the menopause. Observations mentioned here this morning indicate that in mice treated with radiation a dis-

integration of the follicular apparatus occurs but estrus continues, due to the fact that sufficient estrogenic hormone is elaborated by the parenchymatous cell changes to support this function. We know of course that there occurs a marked decrease in the estrogenic output in castrates. Nevertheless is it not possible that in women treated much less than would be normal, let us say for a carcinoma, but sufficient to cause complete and permanent cessation of menstruation, a change occurs similar to that described for the laboratory animal? I should like to know whether either of the essayists has had the opportunity of studying human ovarian tissue from women who have been subjected to *average* castration doses of x-ray.

DR. GEORGE W. CORNER, ROCHESTER, N. Y.—Is it not possible that the origin of the new cells of the granulosa type is from surviving undifferentiated cortical tissue? It has been noted in experiments on sex reversal in salamanders, that when the male gonad is changed into an ovary, the newly-differentiated cells of ovarian character come from the undifferentiated cortex of the original gonad.

I should like to ask Geist whether he has evidence of the production of corpus luteum hormone by the cells which he described by the word "luteinized"; such evidence would be, for example, a progestational reaction of the endometrium or a mucification of the vaginal epithelium, indicating an interaction of progesterone with estrogen.

DR. GEIST (closing).—In answer to a question that Miller raised, we are not in a position at the moment to report on the status of postradiation ovaries in the human female. However, we have evidence to show that in a large group of cases the estrous phenomena may persist for as long as nine months, as indicated by a normal estrogen excretion and a positive vaginal smear. We know, however, that the follicular apparatus of the ovary is destroyed, but there is still parenchymal tissue which may produce this substance and maintain estrus for three to nine months. We do know that if such rayed ovaries are removed, estrus promptly ceases. This strongly suggests that the rayed ovaries produced sufficient estrogen to cause the estrous phenomena.

Corner raised a question about the surface epithelium in the mice. Parks, in his interpretation of the early radiation changes, thought that in radiated immature mice these parenchymatous changes might be due to surface invasion. In the mature x-rayed mice he found no such invasion. We believe that the surface epithelium in the human being takes no part in the formation of the parenchyma of the ovary. It is formed by a transition in situ of the original mesenchyme, so that theoretically we believe, since the study of the rayed mouse ovary, that the surface of the ovary would be in no way concerned with parenchymal changes that we expect sometimes to find in the human being.

DR. TRAUT (closing).—I have been asked for a word as to how the ovarian tumors are produced in the mouse. In our series they were rayed before the first estrus had taken place and were given about 400 units over the whole body, including the hypophysis. At varying periods of time, usually not less than 300 or 400 days, we began to get adenomatous changes in the ovary which might be called tumor formation. The granulosa cell formation came at a late period, usually 800 to 1,000 days after radiation.

The fact that the radiation in mice produces tumors and the fact that x-ray may stimulate certain cells in the ovary to proliferate, may have some importance in the human being. We have seen several suggestive instances since Butterworth and I gave our paper two years ago. We have had called to our attention four patients who had been castrated by deep x-ray therapy and then subsequently had developed granulosa cell tumor. However, we shall have to have a great deal more experience before we can draw conclusions as to the importance of x-ray therapy as a causal factor in producing granulosa tumors in the human being.

In answer to one of Corner's questions, many of the tumors do produce progesterone. With certain of the mouse tumors we have observed definite secretory phases occurring in the endometrium after it has undergone hypertrophy. In addition the secretory phase of the endometrium has been reported as occurring with luteinized tumors in the human being, notably those of Novak and Johnston and Stabler.

VASCULAR LESIONS IN THE DECIDUA BASALIS*

JOHN L. MCKELVEY, M.D., C.M., MINNEAPOLIS, MINN.

(From the Department of Obstetrics and Gynecology, University of Minnesota)

THE condition and function of the maternal vascular system in pregnancy is constantly attracting more attention. Information is now available which demonstrates gross disturbances in this system in normal pregnancy. The mechanism by which this is brought about is not as yet clear. Nor is there a proved explanation of the reason for the extension of this disturbance to the degree of the production of a pathologic state in a minority of individuals and its absence in the majority, although hereditary factors seem to partially explain certain types of response, such as the production of arteriolosclerosis. The end results of permanent arteriolar damage[1] are understood and have been demonstrated to be indistinguishable from those of essential hypertension occurring without the pregnancy factor. The etiology of the acute toxemias, i.e., pre-eclampsia and eclampsia, is still far from solution. Two of the fundamental features of these disturbances, edema and hypertension, are related to vascular function. All of this suggests the value of studies of the vascular system in both normal and abnormal pregnancies.

The morphology of the vessels near the placenta is of interest, but one must be cautious in interpreting these findings into generalizations for the vascular system as a whole. Due to the absence of capillaries between the arterial and the venous circulations in this area, special circumstances are present which might be expected to have results similar to those about an arteriovenous fistula.[6, 7] In the second place, it has been assumed that vascular lesions here are associated with continuous exposure to excessive concentrations of toxic substances formed in the fetal portion of the placenta.[4] It has recently been shown that these vessels are arterioles. No one has as yet demonstrated a back flow of intervillous space blood into these arterioles and until such time as this is proved, it might be wiser to assume a continuous blood flow in the direction of the intervillous space.

It is, however, from the vessels of the decidua basalis that that part of the hemorrhage arises which lifts off the placenta from the uterine wall in premature separation of the normally implanted placenta. Curiously enough, no one seems to have given any attention to the question as to whether this hemorrhage is arterial or venous in origin. Disturbances in the vessels here have been described[4] but these descriptions have been incomplete.

The object of this study is to report upon the findings in the arterioles of the decidua basalis in normal and a few abnormal pregnancies. Since the material has been obtained from sections of placentas, the portion

*Read (by invitation) at the Sixty-Fourth Annual Meeting of the American Gynecological Society, White Sulphur Springs, W. Va., May 22 to 24, 1939.

of the arteriole studied is that above the musculature and in most cases confined to that portion which lies in what Grosser called the "Durchdringungszone." The material has been collected over a period of years by setting aside the routine sections of the placentas which showed vessels. The original material was taken as far away as possible from the margin of the placenta and any sections which showed evidence characteristic of the marginal portion of the placenta were discarded. Only occasional attempts were made to specifically obtain sections through vessels. Fetal vessels entering the decidua were excluded from the study. These retain their muscular walls in contradistinction to the maternal arterioles where formed walls are almost always absent. The fetal vessels pass through this area with surprisingly little change, while the maternal vessels are grossly affected.

Because of the level at which the vessels were studied, it was found impossible to differentiate veins from arteries in most cases. In the vast majority of the vessels found there was great dilatation of the lumen and the vessel wall contained no structures to allow such a differentiation. Spanner[2] has, in a most detailed study, demonstrated the fact that only arterioles penetrate to the upper part of the decidua basalis and enter the intervillous space in the majority of the maternal placental surface, while all venous return occurs through the marginal sinuses which lie in an area within 2 cm. of the circumference. If this be true, as there is every reason to believe, then the vessels with which we are dealing are arterioles. It will be assumed in this paper that this is correct. Stieve[3] makes the bold statement that occasional veins leave the intervillous space through any part of the placenta. The corrosion preparations of Spanner are so convincing that Stieve's unsupported statement is insufficient to throw doubt upon their validity. The studies to be presented show a continuous series of changes in similar vessels. It should be made clear, however, that there is nothing in the structure of these vessels to allow a decision as to their place in the vascular system.

Vessels with intact muscular media are occasionally encountered. These are for the most part small arterioles, and it is suggested that they represent the arterioles given off to supply the decidua and do not enter the intervillous space. Others in the neighborhood of anchoring villi may be readily recognized as fetal vessels.

Changes in the vessels of the decidua basalis have been described by numerous observers and attempts have been made to relate these to ferments or chemical products from degenerating fetal portions of the placenta.[4] The older literature is covered by Grosser[5] who also reproduces photomicrographs of some of the lesions to be described.

The arterioles which conduct blood to the intervillous space show, at the level described above, extensive coiling. Many cross-sections of the same vessel are to be seen in a single section. In the vast majority there is no evidence of a muscular media or an adventitia, and the wall is composed solely of decidua, chorionic cells, a mixture of these in various stages of degeneration or a peculiar hyaline acellular, ground-substance-like material which has been called fibrinoid and which stains densely pink with eosin. The wall of the arteriole, then, does not have the

supporting structures usual to the arteriole elsewhere. The majority of vessels at this level show advanced degrees of replacement of the cellular surrounding structures by the peculiar fibrinoid material.

This fibrinoid material has a concentric distribution which is unmistakable. It forms rings of varying thickness about the vessel lumen. It may have a well-defined margin against the surrounding cells, but most often connects directly with a similar appearing substance which spreads out in a network between the decidual or chorionic cells and may become continuous with the massive collections of similar substance just beneath the intervillous space. This material in the vessel wall gives the impression of being solid substance. Fibrils are not seen. The surrounding cells may show no evidence of degeneration.

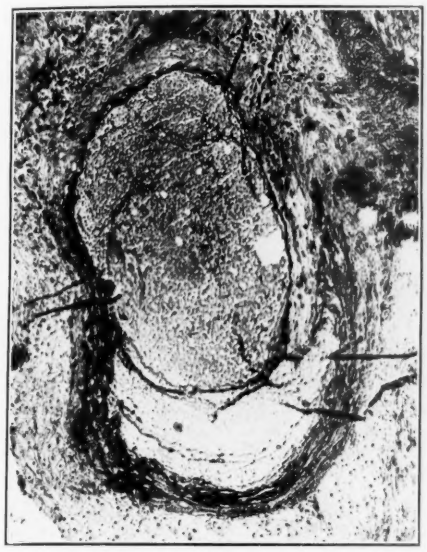

Fig. 1.

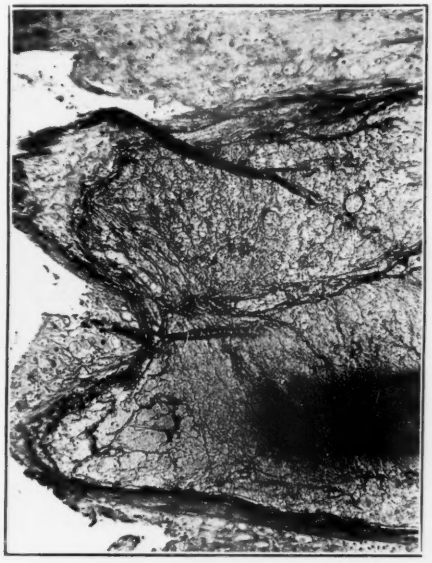

Fig. 2.

Fig. 1.—Arteriole from the decidua basalis of normal pregnancy. There is dilatation, laying down of fibrinoid material in the wall and aneurysmal dilatation at one portion. Note the concentric arrangement of the fibrinoid material and the generally sharp line of demarcation between this material and the surrounding decidua. ×65.

Fig. 2.—Arteriole from the decidua basalis of normal pregnancy. Enormous dilatation with early aneurysmal dilatation and early thrombosis. ×65.

In other vessels the surrounding area appears to be diffusely infiltrated by a plasmalike material which invades peripherally and destroys the enmeshed chorionic or decidual cells. This seems to decrease in concentration and necrotizing influence as it proceeds further from the vessel.

The endothelium of the vessel is most often absent in the vessels at this level at term. The greater the degree of change in the vessel wall, the less endothelium is seen. Occasionally, areas of round cell infiltration (Fig. 3) or massive necrosis of the decidua are seen. These are not typical of the lesion.

The lumina of these vessels are very large (Fig. 2). That this dilatation does not represent a physiologic response seems evident from the character of the vessel wall and from the fact that aneurysmal dilata-

tions (Fig. 1) of portions of the circumference with splitting of the fibrinoid material into separated layers occur frequently. All degrees of this dilatation are seen until premature separation of the placenta occurs (Fig. 6) when enormous dilatation may be demonstrated.

There is no evidence that this lesion is necessarily associated with clinical evidence of toxemia. For practical purposes all of the material studied was from the placentas of clinically normal pregnancies. The exceptions are noted. Nor is there any evidence of excessive so-called infarction of the placenta in the immediate neighborhood of these lesions.

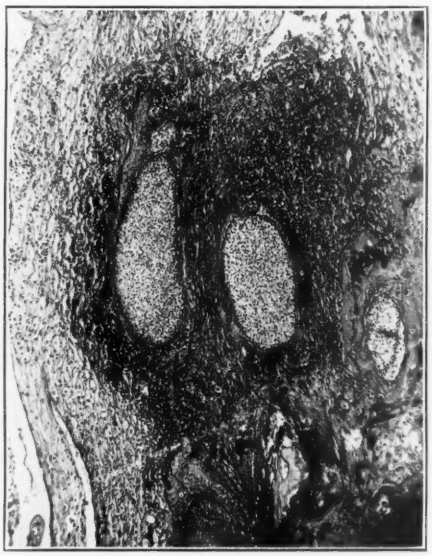

Fig. 3.

Fig. 4.

Fig. 3.—Arteriole from the decidua basalis of normal pregnancy. Laying down of fibrinoid material in the wall. Extensive round cell infiltration into the surrounding decidua. ×65.

Fig. 4.—Arteriole from the decidua basalis of normal pregnancy. Marked dilatation and coiling of the vessel. The portion of the vessel seen in the center shows splitting of the fibrinoid wall with pools of blood plasma. ×65.

If, as Spanner states, these are arterioles, there is little reason to assume a retrograde flow from the intervillous space. Under these circumstances the blood bathing the arteriolar wall is general systemic blood and not that from the intervillous space.

These lesions are not limited to the placenta at term. Grosser states that they occur in early pregnancy and they have been found in this series as early as the seventh month. No evidence has been found to prove that invading chorionic epithelium has an etiologic relationship, though this is possible. Occasionally, chorionic cells are seen attached to the wall in the lumen and they may, of course, surround the vessel. The concentric arrangement of the fibrinoid material strongly suggests a central origin.

However, it is clear that the vessels at this level, which are apparently arterioles, are damaged in normal pregnancy. The damage is associated with the laying down of fibrinoid material in the wall. That this is not

an efficient structure is manifested in the great dilatation of the lumen and the appearance of aneurysmal dilatations with breaking up of the wall at this point.

The dilatation of the apparently weakened vessel is a dangerous process and the question of its mechanism naturally arises. It occurs in the absence of an increased systemic pressure. It is possible that it represents a response to normal pressure in a weakened vessel. One other explanation is suggested as a likely cause. Burwell and his coworkers[6, 7] have drawn attention to the fact that the intervillous space is a modified arteriovenous fistula. No capillaries are interposed between the arterial and venous circulations. That this arteriovenous fistula effect is modified is shown by the absence of sudden elevations of systemic pressures at delivery when the fistula is removed. Many other changes in pregnancy as increased blood volume, the placental bruit, and increased venous pressure in the lower extremities are suggestively similar to those occurring in clinical or experimental arteriovenous fistula.

In the presence of an arteriovenous fistula there is a readily understandable dilatation of adjacent veins. Halsted[9] pointed out that there was also a dilatation of the proximal artery. The literature is covered by Holman.[8] The mechanism of this is unexplained. The similarity of the result here and in the vessels of the decidua basalis was pointed out by Burwell, and while it is not proved, the author is inclined to accept this as a likely relationship. No exact morphologic studies of the vessels in the region of an experimental or clinical arteriovenous fistula can be found in the literature so that nothing can be said of the relationship between the modified arteriovenous fistula and the deposition of the fibrinoid material in the arteriolar walls.

This dilatation of the arteriole may proceed to great lengths. Fig. 4 shows the vessels from a placenta at term in a normal, nontoxemic pregnancy. The villi adjacent to it show no evidence of infarction. There is normal decidua basalis on either side. The vessels are twisted and enormously dilated. The whole wall is composed of fibrinoid material and contains neither decidua nor chorionic cells. No endothelium remains in the vessels. That portion of the vessel whose whole circumference is seen in the center of Fig. 4 shows its walls to be torn apart by blood plasma which has collected in small lakes. The blood in the lumen shows no evidence of thrombosis.

A further stage of this is seen in Fig. 5 which is also derived from the placenta of a normal term pregnancy. This presented a small reddish brown nodule on the maternal surface of the placenta. On section it shows greatly dilated vessels whose walls are made up of fibrinoid and are ruptured. Old, partly hemolyzed blood lies in the fibrinoid material surrounding the vessels. Immediately above this area the villi are packed together, are relatively avascular, and their epithelium is proliferated. Immediately below is a small collection of blood which lies free beneath the tissue. This represents what might be called a subclinical or miniature premature separation of the normally implanted placenta.

It is extraordinarily difficult to get satisfactory sections for study of the vessels in fully developed premature separation of the normally implanted placenta. There is widespread infarction with destruction of tissue which leads to poor staining. Fig. 6 shows the remains of such vessels from a small area of premature separation. One may be seen to open into the main blood mass producing the separation. The vessels are greatly dilated as those described above and show remnants of the fibrinoid material. There is overlying compression of the villi with early infarct formation, but whether this is related as cause or effect is open to doubt. Under any circumstances the vascular form appears to be similar to that described above.

Fig. 5.

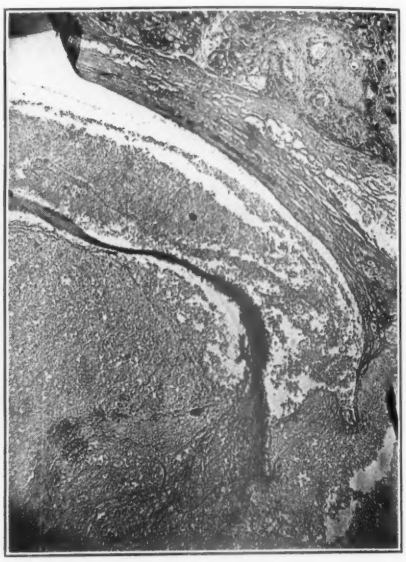

Fig. 6.

Fig. 5.—Arteriole from the decidua basalis of normal pregnancy. Grossly this presented as a small brownish area on the maternal surface of the placenta. On one side may be seen early infarct formation. On the other, there is a mass of fresh blood which has indented the maternal surface. Between these the decidua has been destroyed and the dilated vessels have collapsed. This represents the condition described as miniature premature separation of the normally implanted placenta. ×65.

Fig. 6.—Decidua basalis from the margin of a small area of premature separation. The main blood mass is seen and above it, the remains of a vessel at or very close to the area of rupture. ×65.

Thus there appears to be a series of changes which occur in what are presumed to be arterioles in the upper portion of the decidua basalis. These begin with replacement of the wall and endothelium by fibrinoid. Gradually, dilatation of the lumen and extension of the fibrinoid with increase in the coiling of the vessel lead to rupture. Blood is extruded. Depending upon the amount of this hemorrhage, varying degrees of premature separation occur. The smallest of these produces a condition described as miniature premature separation. This produces no clinical symptoms. It offers the best available material for the study of the mehanism of premature separation. Larger hemorrhages lead to clinical premature separation.

Various degrees of these changes occur in the majority of arterioles of the decidua basalis and their occurrence is independent of the presence of the pregnancy toxemias. In the early stages at least, there is no evidence to support an etiologic relationship to infarction of the placenta. Such relationship in clinical premature separation is not yet proved, though possible. The modified arteriovenous aneurysm effect of the intervillous space is again suggested as a causal factor in the production of dilatation of these vessels. Its relationship to the other changes described is not clear.

It is suggested, then, that the basic circumstances inherent in premature separation of the placenta are present in most if not all human placentas. The degree of extension of this process determines the appearance or nonappearance of clinical premature separation.

CONCLUSIONS

1. In association with normal pregnancy, lesions in the arterioles of the upper part of the decidua basalis frequently occur. These changes include the laying down of fibrinoid material in the wall, dilatation and aneurysmal dilatation. They are not necessarily associated with pregnancy toxemia nor with placental infarcts.

2. A series of these changes may be traced from mild lesions to rupture with the production of miniature or clinical premature separation of the normally implanted placenta.

3. Premature separation of the normally implanted placenta is an extension of changes in the arterioles probably present in every human placenta. One of the factors in this extension is the arteriolar dilatation associated with the modified arteriovenous aneurysm effect of the intervillous space.

REFERENCES

(1) *McKelvey, J. L., and McMahon, H. E.:* Surg. Gynec. Obst. **60:** 1, 1935. (2) *Spanner, L.:* Ztschr. f. Anat. u. Entwicklungsch. **105:** 163, 1936. (3) *Stieve, H.:* Zentralbl. f. Gynäk. **59:** 434, 1935. (4) *Bartholomew, R. A., and Kracke, R. R.:* Am. J. Obst. & Gynec. **24:** 797, 1932. (5) *Grosser, O.:* Frühentwicklung, Eihautbildung und Placentation des Menschen und der Säugetiere, p. 376, 1927. (6) *Burwell, C. Sidney, et al.:* Arch. Int. Med. **62:** 979, 1938. (7) *Burwell, C. Sidney:* Am. J. M. Sc. **195:** 1, 1938. (8) *Holman, Emil:* Arteriovenous Aneurysm, New York, 1937, The Macmillan Company. (9) *Halsted, W. S.:* Proc. Nat. Acad. Sc. **5:** 76, 1919.

DISCUSSION

DR. RUDOLPH A. BARTHOLOMEW, Atlanta, Ga.—McKelvey contends there are certain fundamental structural changes and conditions of the maternal arterioles in the decidua basalis which predispose to and cause premature separation of the placenta, not only in subclinical or miniature form but in more severe abruptio or ablatio form. He also contends that such separation occurs without any evidence of toxemia or adjacent infarction.

It seems reasonable to believe that the dilated terminations of the maternal arterioles, the thinning of their walls, the loss of endothelial lining and the presence of the so-called fibrinoid or hyaline substance about the vessels and in the decidua, have existed since the early stage of formation of the placenta, and represent the final result of the interaction of the invasive trophoblast and the maternal decidua and arterioles.

When one considers the comparatively fragile attachment of the placenta to the uterine wall, it is surprising that we do not more often see evidences of recent or old separation of the placenta when the specimen is examined. If the structural changes mentioned, predisposed to hemorrhage to the extent claimed by the author, it would seem that clinical degrees of separation of the placenta would occur much more often than is actually the case, and there would be a notable absence of associated toxemia. On the contrary, there has always been emphasized a strikingly frequent association of toxemia.

It has been my observation, that if one carefully examines the fixed placenta from a case of abruptio placentae, one will almost invariably find an area of black or brown acute infarction on or just beneath the maternal surface, where the maternal clot has indented the placental substance. The evident age of the necrosis in the infarct, in contrast to that of the fresh hemorrhage, is sufficient proof that the infarction could not have been caused by the hemorrhage.

Theoretically, clinical degrees of hemorrhage in the decidua basalis must result from the trauma, venous engorgement from kinking of the broad ligament of the overrotated uterus, or damage to the maternal vessels from toxic protein split products of acute placental infarction. The first two are rare. The last has been produced experimentally by Hofbauer by injection of histamine in pregnant guinea pigs. The almost invariable finding of acute placental infarction and toxemia with clinical degrees of premature separation of the placenta, leads me to believe that placental infarction is the cause, rather than structural changes in the maternal arterioles.

DR. JAMES RAGLAN MILLER, HARTFORD, CONN.—On reviewing sections of placentas which I have been able to study since reading McKelvey's paper I have been unable as yet to demonstrate the lesions which he has shown. In a recent case of partial premature separation with external bleeding, I could demonstrate blood vessels in the decidua close to the intravillous spaces and distal to areas of hemorrhage which appeared to be on the maternal side of Nitabuch's fibrin layer. These vessels had for walls a definite single layer of endothelium and showed no abnormal changes, and are probably to be classed as venous capillaries.

With the Masson stain, Nitabuch's so-called fibrin layer stains deep red, suggesting that it consists of degenerated decidual cells. In recent years the finer anatomy and histology of blood vessels have developed on the basis of newer technique which should be applied to the study of the vessels of the placenta. Confirmation is needed, for example, of the observation that in the endometrial basal arteries of the nonpregnant uterus, there is an absence of elastic fibers, though they are present both above and below this zone. It is this layer of blood vessels which appears to be concerned in the mechanism of menstruation in the last forty-eight hours before bleeding occurs. It is also this layer of blood vessels in which we might expect to find changes productive of premature separation.

Until the modern methods of study have been applied to the finer histology of the blood vessels involved, it would seem too early to do more than speculate concerning the part which toxemia may play in premature separation, and perhaps, even to speculate on the mechanism of such hemorrhages.

DR. OTTO H. SCHWARZ, ST. LOUIS, MO.—Studies made by us in 1923 were from material secured at autopsy before the patient was delivered, or from the placenta obtained by cesarean section. In most cases that had definite hypertension the changes in the inner third of the arterioles were very striking. They showed arteriosclerosis with some destruction of the intima. We also studied the vessels of the basalis and in several instances we saw excessive dilatation with only a strand of the vessel remaining. At that time we suggested that these aneurysmal dilatations might be responsible for some cases of placental apoplexy, but not all. We suggested also that this might result from a marked hypertension that existed in these patients before they died.

DR. McKELVEY (closing).—Both Bartholomew and Miller have raised the question of the relationship of toxemic effects in the production of disturbances in

systemic pressure and its effect in the rupture of these vessels. I can only say that I have no evidence whatever to lead me to any explanation of the relationship between disturbed systemic pressure and the changes in these vessels, although one might of course assume that that occurred. Yet it is always dangerous to accept obvious explanations. Something else is going on, and the changes in the pressure within these arterioles in relation to the changes of the vessels in arteriovenous fistulas would lead one to suspect that here is an area where systemic pressure is at its lowest instead of at its highest. I have no explanation for the incidence of increased pressure, but that that is a well-recognized fact goes without saying. The cases that have worried us are the ones where separation occurs without hypertension.

Bartholomew has referred to the possible relationship of the infarcts. My main object is to present the changes in the vessels in normal pregnancy and those without demonstrable infarction. The first four were taken from areas which showed no morphologic or gross evidence of infarction around those regions. In my opinion, the age of the infarction in premature separation, and the presumption that it preceded the vascular lesion are open to some doubt, but we cannot rule out an infarction effect as a final throwing over of a potential vascular lesion into a clinical lesion.

Miller had my paper for only a short time, and it is a fact that one may search many sections without finding any vessels. My material has been collected over a period of four to six years, during which time we simply put aside those sections which do show vessels. I have somewhere in the neighborhood of a couple of hundred in which the vessels demonstrate lesions.

It is also true that there is no necessary relationship between the degree of the lesions in various vessels of the same placenta. This peculiar spotty effect of vascular lesions is characteristic of arteriolosclerosis that is seen elewhere in the body, and I believe that we have here a similar effect. There appears to be an element of chance in these lesions. The fact that there is a premature separation in some vessels is not evidence that there will be destruction of other vessels.

The paper Schwarz spoke of, as I remember, dealt primarily with the vessels of the uterine musculature and not those close to the entrance into the intervillous space. The vessels in the upper part of the decidua basalis have no wall of any sort except endothelium and a basal membrane.

CHORIOEPITHELIOMA*

A Clinical and Pathological Study

K. M. Wilson, M.D., Rochester, N. Y.

(From the Department of Obstetrics and Gynecology, the University of Rochester School of Medicine and Dentistry)

CHORIOEPITHELIOMA is ordinarily regarded as one of the most malignant epithelial tumors with which we have to deal, but at the same time it is also a type of tumor which at times presents quite extraordinary vagaries in its growth and general course of development. In considering some of its characteristics, it is interesting to recall that it originates in cells which normally possess highly invasive powers, and which in addition may even be broken off from the developing ovum and be carried by the blood stream as minute cellular emboli to distant parts of the body, the so-called deportation of chorionic villi. How long these invading or transported fetal cells persist after the pregnancy from which they originate comes to an end is unknown. In general, they probably degenerate early, but on the other hand may occasionally persist for a long period of time, even for years, as is evidenced by the development of a chorioepithelioma months or years after an hydatid mole or other form of pregnancy. With these characteristics of normal trophoblastic cells in mind, the wonder is that malignant change does not occur more often than is actually the case.

The series of chorioepitheliomas herewith presented, though small, illustrates rather well both the usual characteristics of this type of tumor and some of the less frequently observed features of this relatively rare type of tumor.

Case 1.—(Unit No. 35102.) J. G., aged 24 years, para ii, was admitted May 12, 1930 with active vaginal bleeding present for ten days. Hb. 28 per cent, red blood cells 2,000,000. Menstruated last on February 15. Fundus of uterus at the level of the umbilicus. Transfused and hydatid mole removed by vaginal route. No ovarian enlargement noted. Microscopic examination of the tissue removed showed the typical picture of hydatid mole with no appearance of malignancy. June 7 on account of recurrence of moderate vaginal bleeding, curettage was done. Curettings revealed normal regenerating endometrium but also a few microscopic fragments of mole which were not considered malignant. Friedman test positive with 5 c.c. of urine, becoming negative after forty-eight hours. July 15, recurrence of moderate bleeding, diagnostic curettage. Curettings scanty and showed normal endometrium with no fetal tissue. Friedman test negative. Normal menstruation re-established in August and continued so for a year. Aug. 26, 1931 readmitted on account of slight persistent bleeding present for three weeks. General and pelvic examination revealed no abnormalities. Diagnostic curettage done. Curettings scanty and microscopically showed normal endometrium. Oct. 8, 1931, menstruation delayed eight days but then occurred normally. Friedman test negative. Nov. 5, 1931 seen in outpatient department and condition appeared satisfactory. Pelvic

*Read at the Sixty-Fourth Annual Meeting of the American Gynecological Society, White Sulphur Springs, W. Va., May 22 to 24, 1939.

examination negative. December 26 admitted to hospital, critically ill, with history of cough and bloody sputum for the past week. In addition a rounded tumor nodule 4 cm. in diameter discovered in anterior vaginal wall. Radiograph of chest showed extensive metastatic involvement of both lungs. Friedman test positive with 5 c.c. of urine. Died Dec. 30, 1931. Autopsy showed chorioepithelioma of uterus with metastases to vagina, lungs, and kidneys. No lymph node involvement.

Fig. 1.—Pelvic organs removed from Case 1 at autopsy. The uterine tumor is embedded in the wall of the uterus and is covered by normal endometrium so that a diagnostic curettage would be very misleading. The curette would remove no tumor tissue unless it were thrust deeply into the tumor mass. Note the vaginal metastases.

Comment.—Unless this tumor followed the unusually rapid course of two and one-half months from beginning to end, we are forced to the conclusion that the result of the Friedman rabbit ovulation test was not only of no help from the diagnostic standpoint, but was actually misleading, as a negative result was obtained at a time when it seems reasonable to suppose that this woman harbored an actively developing tumor though presenting no clinical signs or symptoms.

Chorioepithelioma being a highly vascular tumor, with numerous blood spaces within it, ordinarily metastasizes by the blood stream, hence secondary lesions about the vagina or vulva, or in the lungs, are frequently seen. At the same time, as the cells possess such highly invasive properties, the uterine wall may be actually perforated as the result of

direct extension of the growth and dissemination throughout the peritoneal cavity occurs as a result of this. Under such circumstances too there may be a fatal intraperitoneal hemorrhage. This mode of extension is well illustrated in the second case in this series.

CASE 2.—(Unit No. 20593.) F. D., aged 38 years, para ii, grav. v. Admitted Dec. 27, 1928. In September, 1928 had completion of a two months' spontaneous, incomplete abortion in another hospital. Discharged after five days. Following this had irregular episodes of bleeding with a profuse hemorrhage on December 1.

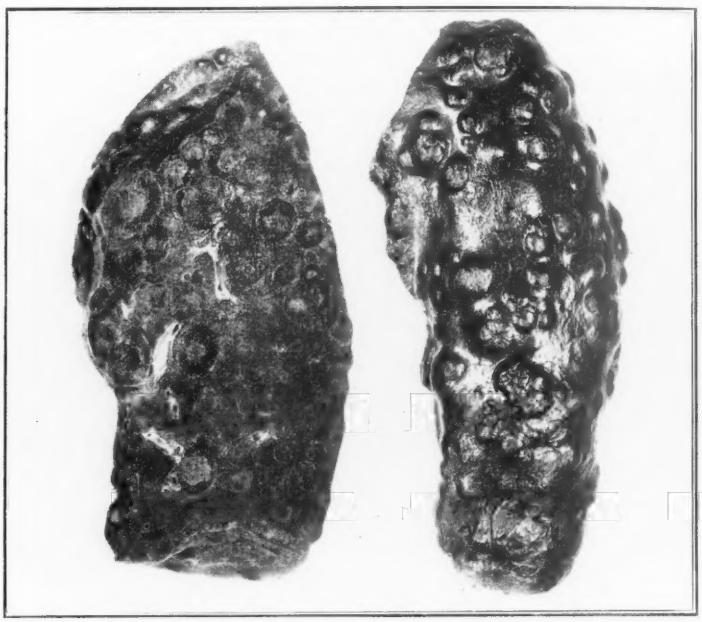

Fig. 2.—The lungs from Case 1 showing extensive nodular metastases.

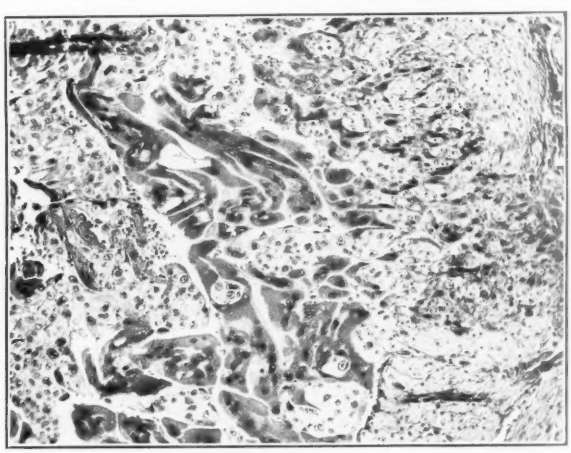

Fig. 3.—The microscopic picture of the uterine tumor from Case 1 shows active growth of both types of cells.

Uterus and vagina packed by her physician and at the same time some tissue obtained for examination which showed definite chorioepithelioma. On admission to our service Hb. 50 per cent, red blood count 2,770,000. Radiograph of chest negative. Pelvic examination showed uterus enlarged to the size of a two months' pregnancy, but freely movable, slight bleeding, no ovarian enlargement. Transfusions given and other antianemic therapy. January 7 operation. On opening the abdomen considerable chocolate colored material escaped and numerous adhesions were encountered. When the uterus was exposed, a small friable bleeding nodule was found at the left uterine cornu, evidently a direct extension of the tumor through the uterine wall. As there were extensive peritoneal implants, a radical

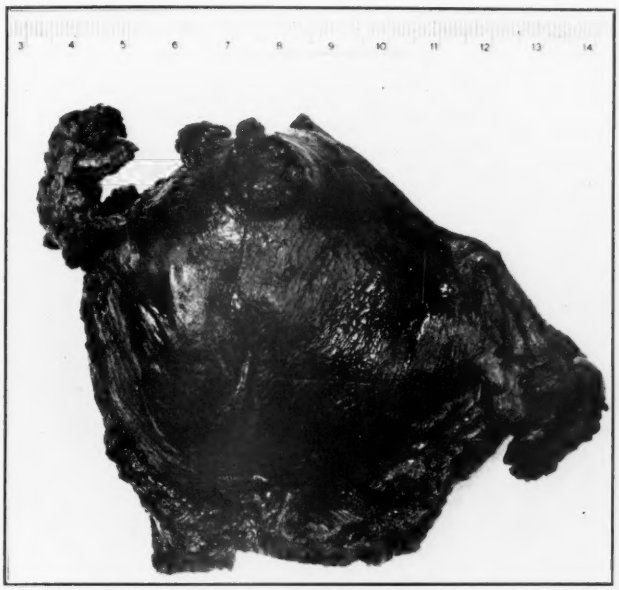

Fig. 4.—The uterus from Case 2 showing perforation of the uterine wall by extension of the tumor growth. This resulted in extensive involvement of the peritoneum.

Fig. 5.—The uterus from Case 2 showing the main growth in interior of the uterus.

operation was obviously useless, so a subtotal hysterectomy with removal of both appendages was carried out as a purely palliative measure to prevent further bleeding. Microscopic examination of the tumor showed the characteristic appearance of a rapidly growing chorioepithelioma, with no significant ovarian changes noted. Postoperative convalescence uneventful. Deep x-ray therapy carried out as a further palliative measure. February 5, radiograph revealed metastatic area in right lung; deep x-ray therapy directed towards this. March 26, extension of pulmonary lesions observed but no subjective symptoms. April 30, cough with bloody expectoration, rapid downhill course, and died at home June 3, 1929. No autopsy.

Among the peculiarities of this type of tumor is the fact that at times no primary uterine tumor may be demonstrable, and yet single or multiple growths may be found in other parts of the body and cause death. In explaining the origin of these so-called "ectopic chorioepitheliomas," apart from their occasional teratomatous origin, several possibilities must be considered. According to Schmorl, such an ectopic tumor might arise from an hydatid mole or other form of pregnancy in which a malignant change had taken place in some of the trophoblastic cells, possibly in only a very small area of the placenta, before the ovum was expelled or removed from the uterus. These malignant cells if transported elsewhere by the blood stream, could obviously become metastatic growths, and yet no tumor would be found in the uterus. Marchand, Pick, and others believe that these ectopic tumors may arise as the result of malignant change in the trophoblastic cells transported to other portions of the body in the course of a perfectly normal pregnancy. Still another possibility in regard to the origin of the ectopic tumor is to be found in the case presented by Novak and Koff in which the primary uterine tumor disappeared but the patient died as the result of metastases. A most unusual example of ectopic chorioepithelioma is that reported by Sears in which the tumor was located in the jejunum, and developed nearly three years after the last probable preceding pregnancy.

CASE 3.—(An example of ectopic chorioepithelioma.) (Unit No. 106899.) E. S., aged 28 years, para ii. Admitted Sept. 15, 1935 after a sudden onset of cerebral symptoms, headache, vomiting, irrational. Lumbar puncture showed blood in cerebrospinal fluid. Last pregnancy a normal full-term delivery one year previous to admission. One year prior to that a possible mole removed from uterus. For six months prior to admission there had been slight persistent vaginal bleeding but no marked anemia developed. Pelvic examination revealed a slightly enlarged retroverted uterus, ovaries not enlarged. Radiograph of chest negative. September 17 and September 27 Friedman test positive with 5 c.c. of urine. September 28, diagnostic curettage. The curettings presented an appearance suggestive of decidua and yet not typical. No trophoblastic cells were found. On the basis of the positive Friedman test together with the other clinical findings, a tentative diagnosis of chorioepithelioma of the brain was made. Oct. 4, craniotomy and decompression (Dr. Van Wagenen). The general condition improved following the decompression, and she was discharged on October 19. Friedman test remained positive. Died at home Nov. 3, 1935. Autopsy showed chorioepithelioma of brain, lungs, spleen, and kidneys. No evidence of tumor formation in the uterus and no significant findings in the ovaries.

Comment.—In this ectopic chorioepithelioma, it is impossible to say definitely whether there had been a primary uterine tumor which dis-

appeared after metastases had developed, or whether it was an ectopic tumor from the beginning, developing from trophoblastic cells transported during one of her previous pregnancies.

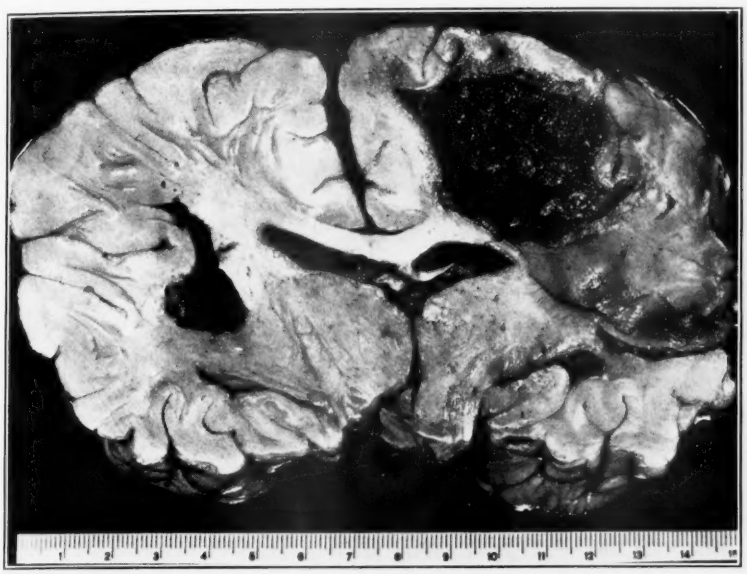

Fig. 6.—The brain from Case 3 showing the ectopic tumor embedded in the brain substance.

Fig. 7.—A metastatic growth in the kidney of Case 3.

CASE 4.—(Unit No. 80606.) F. S., aged 27 years, para i, gravida ii. Admitted July 28, 1936. Last menstrual period April 4. Uterus the size of a three and one-half months' pregnancy, and a large cystic mass discovered adjacent to it. Friedman test positive with 5 c.c. of urine. Diagnosis: Pregnancy with ovarian cystoma. August 1 laparotomy, bilateral cystomas discovered and removed. Uterus of a size corresponding to period of amenorrhea. The cystomas proved to be multilocular "lutein" cystomas. It is interesting to note that embedded in one of these a normal appearing corpus luteum, 3 cm. in diameter, was found. A belated tentative diagnosis of hydatid mole was made. Two days after operation vaginal bleeding and uterine cramps occurred. August 8 removal of hydatid mole, some of the tissue grossly typical, but much of it necrotic and foul smelling.

Microscopic examination of the tissue revealed some typical hydatid vesicles, but in addition such extensive proliferative changes were noted in some of the trophoblastic masses involving in particular the Langhans cells that the additional diagnosis of chorioepithelioma was made. August 14 chest and skull radiographs negative. August 21 total hysterectomy. On opening the uterus after its removal, a

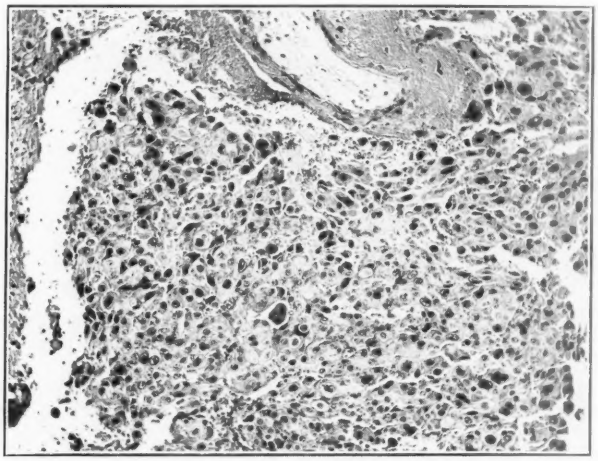

Fig. 8.—Microscopic picture of a fragment of the mole from Case 4 on which a diagnosis of chorioepithelioma was based. Note the extensive and irregular proliferation, with anaplasia, involving in particular the Langhans cells.

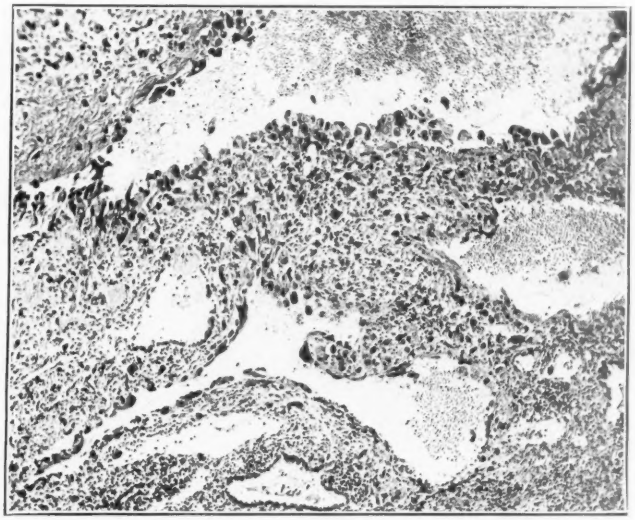

Fig. 9.—Microscopic picture of the uterine tumor from Case 4. Note both types of cells surrounding large blood spaces. The tumor is embedded in the uterine wall and is partially covered by endometrium which shows relatively normal glands.

reddish tumor mass about 2 cm. in diameter was found in the fundus. This had invaded the uterine wall to some extent. Microscopic study revealed a typical picture of chorioepithelioma with both of the usual types of cells included in its structure. Postoperative convalescence uneventful, and her condition today is excellent.

Repeated observations on the Friedman rabbit ovulation test were made on the urine of this patient and gave rather interesting results both from the diagnostic

as well as the prognostic standpoints. July 28 reaction positive with 5 c.c. After the possibility of hydatid mole was suspected, it was done fractionally and a positive result obtained on various days before the removal of the mole with such small amounts of urine as 0.10, 0.08, and 0.05 c.c. August 13 (after removal of mole) Friedman test positive with 5 c.c. of urine. August 30 (twelve days after hysterectomy) reaction negative with 7 c.c. November 10 reaction positive with 7 c.c. Pelvic examination at this time showed no gross abnormalities and radiograph of chest was negative. Fearing the possibility of a recurrence, she was given deep x-ray therapy to the pelvis through six portals, total dosage 6,600 r. units. Following this the Friedman test became negative and has remained so to date even with as much as 15 c.c. of urine.

Comment.—This is the only patient in our series who showed striking ovarian changes in association with her tumor.

CASE 5.—(Unit No. 140365.) A. K., aged 45 years, para ii. Admitted May 10, 1938. Probable miscarriage at about two months in February. Bleeding continued up to time of admission. On admission Hb. 6 gm., red blood count 2,400,000. Transfusions given. Diagnostic curettage done May 18. Microscopic diagnosis chorioepithelioma. After curettage Friedman test positive with 5 c.c., and 0.5 c.c. of

Fig. 10.—A small collection of tumor cells on the surface of the uterus in Case 4, but still covered by a very thin peritoneal layer.

urine but negative with 0.1 c.c. May 26 operation, panhysterectomy and removal of both appendages. The uterus was a little larger than normal and contained numerous seedling myomas. On opening it a reddish, partially pedunculated tumor 4 cm. in length was found near the fundus. On incising the base of this, there was no gross evidence of invasion of the uterine wall. Postoperative convalescence was uneventful, and her present condition, a year later, is excellent. June 1 (six days postoperative) Friedman test positive with 5 c.c. of urine. June 5 (10 days postoperative) Friedman test negative with 9.0 c.c. of urine, also in successive observations, the last one being Mar. 8, 1939 with 10 c.c.

Comment.—It seems not unlikely that in this case we were dealing with malignant change in a retained fragment of placental tissue remaining after the miscarriage occurring three months previously. There was minimal invasion of the uterine wall, though histologically there was no detectable difference as compared with the other tumors. Biologically, however, there was, and this one was evidently of a lower grade of malignancy. Possibly this might represent also one of the unusual type of tumors which disappear spontaneously.

DISCUSSION

This small series illustrates many of the usual features in connection with chorioepithelioma as well as some of the less frequently encountered variations. Two of the tumors were preceded by hydatid mole, two by abortions, and one by a full-term pregnancy. Fairly wide variations in the time elapsing between the occurrence of the original pregnancy

Fig. 11.—The uterus from Case 5 with a partially pedunculated tumor near the fundus.

Fig. 12.—Microscopic picture of the tumor from Case 5. Note active proliferation of both types of cells, and yet the almost complete absence of invasion of the uterine wall beneath the main tumor. Adjacent to this, however, are small areas which show some invasion of the uterine wall.

and the development of the malignant tumor are also observed. Thus the time range varies from immediate occurrence as in Case 4 to more than a year in Case 1. Two have survived for one and three years, respectively, while the other three died.

The diagnosis of chorioepithelioma is at times an extremely easy one to make, but on the other hand, it may tax the resources of the most

experienced pathologist. The condition will be suspected in the event of persistent bleeding following an hydatid mole or other form of pregnancy, but the early diagnosis of a uterine tumor can only be established by the microscopic study of material from the uterus obtained by diagnostic curettage. Even this may fail. If the tumor be completely embedded in the uterine wall and completely covered by normal endometrium as in our Case 1, tumor tissue will not be removed by the curette and an erroneous diagnosis will be made. Such a relationship of the tumor will, however, be infrequent. The greatest difficulty will arise in connection with the hydatid mole, in arriving at a decision from the material examined as to whether it is benign or whether malignant change has already taken place. This difficulty arises on account of the unusually active proliferation of the trophoblastic cells of the mole, and there may even be some destructive invasion of the uterine wall. Ewing distinguishes between the benign and the malignant mole and states that the differential diagnosis between the two usually presents no difficulty, a view which it is difficult to accept. To the latter he applies the term *chorioadenoma destruens*, but as Novak and Koff point out, it would seem preferable to regard this as a type of chorioepithelioma, definitely malignant, though of a somewhat lower grade of malignancy than other types. This diagnostic problem arose in connection with our Case 4. The unusual degree of trophoblastic proliferation discovered in the tissue of the mole at the time of its removal and which particularly involved the Langhans cells, together with a degree of anaplasia and nuclear changes not ordinarily seen with an hydatid mole, led us to make the diagnosis of malignancy. Further study of the uterus grossly and microscopically after its removal left no doubt as to the correctness of this diagnosis.

The degree of invasiveness has been suggested as a criterion for determining whether a mole is malignant or not. This is of value, but on the other hand, the nonmalignant mole as well as other forms of trophoblastic tissue may invade the uterine wall to a considerable extent, so that at times it is difficult or impossible to arrive at a correct conclusion. If the diagnosis of malignancy is already established, however, the degree of invasiveness will be of great value in grading the tumor as to its degree of malignancy. Thus in Case 5 in our series when minimal invasion of the uterine wall was observed, we had no hesitation in making the diagnosis of chorioepithelioma, but also felt that it was a tumor of relatively low grade malignancy. Possibly a more highly invasive power would have developed later. Unfortunately, the degree of invasiveness cannot be determined until we have the opportunity to study the tumor in situ after the uterus has been removed, so this criterion cannot be used as a diagnostic aid when we are trying to establish a diagnosis from curettings.

One of the interesting biologic reactions of both the hydatid mole and chorioepithelioma is seen in their production of large amounts of the gonad-stimulating hormone somewhat similar in its action to that produced by the anterior lobe of the hypophysis and probably identical with that produced by the ovum in a normal pregnancy. The Aschheim-

Zondek test in mice and the Friedman ovulation test in rabbits, so widely used in the diagnosis of pregnancy, are based on the presence or absence of this hormone in the urine of the individual to be tested. Aschheim was the first to draw attention to the fact that in the presence of hydatid mole or chorioepithelioma, this hormone is found in the urine in unusually large amounts, and he suggested the diagnostic and prognostic value of this finding.

The amount of the hormone present in the urine in either of these conditions is likely to be so great as to give a positive reaction when only a fraction of 1 c.c. of urine is injected into the test animal. Aschheim also carried out quantitative estimations of the hormone content of the urine and came to the conclusion that if on bio-assay a liter of urine contained more than 100,000 mouse units of the hormone, the probabilities would be in favor of hydatid mole or chorioepithelioma being present. He also found, however, that the amount varied according to the size of the mole and that in the small degenerated mole the amount of hormone excreted might not exceed that found in normal pregnancy.

The work of Evans and his colleagues would indicate that further reservations are necessary when these tests are used as diagnostic aids. Thus they found that in normal pregnancy there is a transient period usually about the thirtieth day of the pregnancy when enormous amounts of the chorionic gonadotropic hormone are excreted, and in one instance in their series the total daily excretion amounted to 1,000,000 rat units and a positive test was obtained with 0.005 c.c. of urine. Normally, however, this excretion of large amounts of hormone is a transient phenomenon, and after the peak is reached there is a rapid decrease, until after the sixty-fifth day of the pregnancy when the hormone output was found to be below 10,000 rat units per liter, and continued so until the termination of the pregnancy. From the findings of these observers, it is evident that the demonstration of large amounts of this hormone in the urine does not necessarily warrant the diagnosis of hydatid mole or chorioepithelioma. On the other hand, it does necessitate a careful correlation of the laboratory studies and the clinical findings.

Aschheim states that if the urine of a suspected case gives a negative reaction, chorioepithelioma can be ruled out. That is not entirely correct, as in our Case 1 a negative result was obtained at a time when the tumor must have been developing. The occasional false negative reaction is the chief source of error when these biologic tests are used in the diagnosis of pregnancy, but one would expect such errors to occur less frequently in the case of tumor development. Undoubtedly, greater attention should be paid to the specific gravity of the urine to be tested, as obviously the concentration of the hormone would be less in the urine of low specific gravity. Probably also more accurate information would be obtained by an estimation of the total daily output of the hormone.

With these reservations in mind, it is permissible to say that these biologic reactions may prove to be of considerable diagnostic and prognostic value. Thus a strong positive Aschheim-Zondek or Friedman test, or the demonstration of unusually large amounts of the hormone in a

twenty-four-hour specimen of urine may be helpful in establishing a diagnosis of hydatid mole or chorioepithelioma, provided due consideration be given to the associated clinical findings. These procedures will not, however, enable one to differentiate between the benign mole and the malignant tumor. Persistence of a positive reaction after the removal of a mole or tumor would strongly suggest that the removal had been incomplete or that metastases had occurred, while if a previously positive reaction becomes negative after operation, the assumption would be that the tumor had been completely removed. Repeated observations should be carried out, though, as this may give us the first clue as to a possible recurrence. In our Cases 4 and 5, it was found that the reaction became negative ten and twelve days after operation, respectively. Again, the appearance of a positive reaction, after it had previously become negative, would strongly suggest a recurrence of the tumor.

SUMMARY

Five examples of chorioepithelioma, including one ectopic tumor, are presented. These show variations in their mode of development and extension.

The diagnostic and prognostic value of the biologic reaction in connection with these tumors is discussed.

REFERENCES

Aschheim: Am. J. Obst. & Gynec. **19:** 335, 1930. *Aschheim:* J. A. M. A. **104:** 1324, 1935. *Evans, Kohls, and Wonder:* J. A. M. A. **108:** 287, 1937. *Ewing:* Neoplastic Diseases, ed. 3, 1928. *Marchand:* Ztschr. f. Geburtsh. u. Gynäk. **39:** 173, 1898. *Novak and Koff:* Am. J. Obst. & Gynec. **20:** 153, 1930. *Pick:* Berl. Klin. Wchnschr. **41:** 158, 1904. *Schmorl:* Verhandl. d. deutsch. path. Gesellsch. **8:** 39, 1904. *Sears:* Ann. Surg. **107:** 910, 1933.

DISCUSSION

DR. EMIL NOVAK, Baltimore, Md.—Much stress is being laid on the importance of biologic tests which, although of real value in both diagnosis and prognosis, have their limitations. They will not, for example, distinguish between a benign hydatidiform mole and the malignant chorioepithelioma. The final diagnosis, which alone justifies the report of a case as chorioepithelioma, must be based on the microscopic examination of the tumor. In a recent paper, the statement was made that now since we have available these biologic methods of study, the mortality of chorioepithelioma should be reduced to 5 or 10 per cent, a very far-fetched statement utterly at variance with what we know as to the clinical course.

I need not remind you of the difficulties of microscopic examination in some cases. If a well-preserved villous pattern is found in tissue curetted from the uterus, one should lean backward before making the diagnosis of chorioepithelioma, even though there is much trophoblastic proliferation. On the other hand, when one finds large masses of anaplastic trophoblastic tissue without villi, no other diagnosis than chorioepithelioma would seem justified.

In cases of hydatidiform mole, the vesicles evacuated spontaneously or surgically from the uterine cavity, well away from their blood supply, may seem obviously benign, with little or no trophoblastic activity. A section of the same mole in situ in the uterine wall, will always show much more activity, so that, even though benign, it may be mistaken for chorioepithelioma. Such cases, however, commonly lack the destructive invasion of the uterine muscle by large masses of trophoblast, with the death of the muscle by coagulation necrosis, which characterizes the chorioepithelioma.

I have neevr seen the wisdom of describing an intermediate group, such as the chorioadenoma destruens of Ewing. The malignant characteristics attributed to this group entitle them to inclusion under the designation of chorioepithelioma, though of a lower degree of malignancy than some other types.

DR. BROOKE M. ANSPACH, PHILADELPHIA, PA.—I have observed three cases of chorioepithelioma, each with certain interesting features which apply to the subject matter of Wilson's paper.

CASE 1.—A young woman, in her first pregnancy, had pernicious vomiting. A hysterotomy was performed for hydatidiform mole, and the left ovary, which was cystic and adherent in Douglas' pouch, was removed. Three months later uterine bleeding developed. A curettage revealed proliferating chorionic tissue, but the pathologist was unwilling to make a diagnosis on the histology alone. In the course of three weeks the patient developed a tumor the size of an egg in the left lateral wall of the uterus. At the time of the hysterotomy both ovaries had been enlarged to the size of apples, but at the time of the panhysterectomy in May, the right ovary was reduced to almost less than the average size. This patient is now in excellent health, so that the tumor evidently was of the more benign type. Her first operation had been in January, 1926.

CASE 2.—The patient had had an abortion two months before an acute episode in which she suddenly developed great abdominal pain, difficulty in speech and partial right-sided paralysis. She was evidently losing blood at a rapid rate internally, and the pelvic findings, though inconclusive, suggested a ruptured ectopic. The chorioepithelioma occupied the anterior wall of the uterus and was entirely outside the uterine cavity. The patient recovered, and the aphasic and hemiplegic symptoms grew less. The neurologists were not able to find any evidence of organic brain lesion, so that the cerebral symptoms were ascribed to the loss of blood. The patient is still alive and well.

CASE 3.—This patient, the mother of four children, came in 1935 to Jefferson Hospital with a tumor embedded in the anterior vaginal vault presenting and at the vulvar orifice. There was no evidence of metastasis, and we treated her at first with deep x-ray therapy, which caused the vaginal tumor to shrink rapidly. We got in this case a very decided Friedman reaction from 1/100 *c.c.* of urine. The vaginal growth later recurred and metastases appeared in the lungs. Removal of the uterine tumor was followed by death within a couple of weeks. The nodules were in the uterine wall and not in the uterine cavity, so that there was no uterine bleeding. This evidently was a chorioepithelioma of the very malignant type.

DR. RAYMOND E. WATKINS, PORTLAND, ORE.—Our experience consists of four epitheliomas in the last twelve years, three of which followed hydatidiform mole and the fourth a full-term pregnancy. The first three patients are alive, without recurrence; one 18 months, one 2 years, and one 12 years. The fourth, after full-term pregnancy, is dead.

I should like to present a short history of the last case. A white female, 29 years old, para iv, at term, entered the obstetric ward of the University of Oregon Medical School on March 11, 1936. Her complaint was painless bleeding. A diagnosis of marginal placenta previa was made and labor induced. After five hours she delivered a normal living child without further hemorrhage. The placenta was expelled almost immediately and showed fibrosis at one margin. Her convalescence was normal except that on the third day she passed a clot 10 cm. in diameter.

Thirty-six days after delivery, following a severe uterine hemorrhage, she reentered the hospital in profound shock. At curettage, considerable friable tissue resembling placenta was recovered, and the pathologic diagnosis was probable chorioepithelioma.

The Friedman test was positive. Chest plates were negative. Nine days later, the forty-fifth day post partum, a panhysterectomy was done. A round, purplish gray growth 1.5 cm. in diameter projected into the endometrial cavity from the posterior wall of the uterus. Microscopic sections were diagnosed chorioepithelioma.

To our surprise, routine examination ten days post-operative revealed the presence of a black, soft nodule in the anterior vaginal wall. Following the discovery of this nodule, the Friedman test was found to be strongly positive. Chest plates were repeated but were still normal. A biopsy showed this nodule to be metastatic chorioepithelioma. Roentgen ray therapy was instituted. Forty-one days post-operative the chest plate first revealed an ovoid density suggestive of a newgrowth, and within a short time this process was diffuse throughout both lungs. A productive cough with blood-streaked sputum appeared. Soon afterward another interesting train of symptoms developed, that of difficulty in vision, projectile vomiting, severe headaches, and coma at intervals. A Friedman test of the spinal fluid was positive. She died on August 4, 101 days after her operation, or 146 days post partum.

This case reveals the high degree of malignancy of certain chorioepitheliomas and the wide distribution of their metastatic lesions. It also demonstrates the value of the Friedman test as an aid in the diagnosis and prognosis of this interesting neoplasm. It is interesting to speculate as to whether this chorionic carcinoma was present at the time of delivery.

DR. OTTO H. SCHWARZ, ST. LOUIS, MO.—About five years ago we had an experience with a tumor of this kind. Tissue from this patient, who had been eight weeks pregnant, showed histologic evidence of epithelial proliferation in a very few of the villi. She developed pain in the right lower quadrant and a month later a mass was found. When we operated, we found a mass coming from the upper portion of the uterus at its junction with the tube. This mass had deeply invaded the broad ligament in its posterior portion and could not be entirely removed, but there was nothing in the uterus itself. We found the tumor had its origin in the outer portion of the tube. On histologic examination one would also have had to make a diagnosis of chorioepithelioma, but the patient has now been well for a period of five years. No x-ray was given.

Regarding the Aschheim-Zondek test, it is interesting that one patient presented a rapidly growing uterus and a hydatidiform mole was suspected. The Aschheim-Zondek test was positive, and the surgeon insisted on emptying the uterus. To his surprise and amazement he delivered the patient of three small fetuses.

DR. WILLIAM A. SCOTT, TORONTO, CANADA.—Three previous speakers have shown that a hydatidiform mole may be present in the uterus and curettage not reveal its presence. I wish to record two cases in which this was true.

In the first case, the Aschheim-Zondek test was still positive three weeks after the removal of a mole, but a second curettage revealed no evidence of a chorioepithelioma. Beginning six months later there was slight spotting on three occasions. A second curettage was done, again with negative results, but the Aschheim-Zondek test was still positive. A total hysterectomy was then performed and a chorioepithelioma discovered, embedded in the wall, covered over with a thin layer of muscle as well as by endometrium. The slide showed two definite vesicles, but the histologic picture was a typical choriocarcinoma.

The second patient passed a mole four years ago, and then remained perfectly well until two months ago when she developed a small nodule in the skin on the back. This, on removal, proved to be a choriocarcinoma. Following this she had a slight amount of vaginal bleeding and was curetted, but no evidence of malignancy was found in the curettings. An Aschheim-Zondek test was positive in a dilution of 1:500, but the x-ray of the lungs was negative and no clinical evidences of other metastases were to be found. Therefore, a hysterectomy was done and the tumor was found again embedded deep in the uterine wall and covered with both muscle tissue and endometrium.

DR. WILLIAM P. HEALY, NEW YORK, N. Y.—We are inclined to agree with Wilson's histologic grouping of cases. I have had ten such cases, and they are always extremely malignant and almost always fatal. The two chorioadenoma destruens patients are both alive.

One patient, aged 51 years, came in with vaginal bleeding from a vulvar lesion. A year and a half previously she had been operated upon for ectopic pregnancy. She developed extensive pulmonary involvement and died within three months from the first symptoms. In our experience the choriocarcinoma patients die on an average of five months from the time of the onset of symptoms.

A second patient was also operated upon for ectopic pregnancy. The uterus was subsequently removed because of the pathologic report. Sections showed not only ectopic pregnancy, but also choriocarcinoma. This patient returned with a recurrence in the pelvis and a metastasis in the upper right lobe of the lung. This is the only patient in our series in whom the tumors disappeared under radiation therapy, and she has remained alive now three and a half years since the onset of her disease.

DR. WILSON (closing).—In preparing this paper I was interested to see that only once before in the history of this Society has a paper on this subject been presented, namely by Dr. Vineberg in 1918.

Dr. Novak very properly emphasizes the problem of microscopic diagnosis. Yet I would emphasize that even here difficulty is often encountered in deciding whether a given hydatid mole has become malignant or not. There is practically always unusually active epithelial proliferation even in connection with the benign hydatid mole.

I do not wish to overemphasize the biologic reactions of the chorioepithelioma from the standpoint of diagnosis and prognosis, but on the other hand, in one of my cases and in the one Scott presented, curettage gave no evidence of diagnostic value, in fact was quite misleading. The biologic reaction may be of great diagnostic help when properly correlated with the clinical findings. Furthermore, I believe that the same biologic reactions may be of considerable prognostic value, judging from the way the reaction subsides after the tumors have been removed.

THE ARTERIAL PHENOMENA ASSOCIATED WITH UTERINE BLEEDING IN TUBAL PREGNANCY*

HAROLD O. JONES, B.A., M.D., AND JOHN I. BREWER, M.D., PH.D.,
CHICAGO, ILL.

(From the Department of Gynecology and the Henry Baird Favill Laboratory of St. Luke's Hospital, and the Department of Gynecology of Northwestern University Medical School)

CLINICALLY, in instances of tubal pregnancy, uterine bleeding is one of the most constant symptoms and findings. Fitzgerald and Brewer (1935) in a study of 500 patients with ectopic pregnancy observed that bleeding of some character occurred in 82.4 per cent of these patients. The usual type of bleeding is characterized as a spotting or very moderate flow (71.2 per cent of patients, Fitzgerald and Brewer, 1935). The bleeding usually occurs intermittently or constantly for some time before operative procedures are instituted.

The bleeding has its origin in the uterine decidua in the vast majority of instances, and only rarely does it arise by blood flowing from the tubal lumen into the uterine cavity. The characteristic type of bleeding, spotting, has been explained upon the basis that the decidua desquamates much more slowly than in menstruation. Sampson (1914) and others have demonstrated that the bleeding is, as a rule, reflux flow from the venous spaces in the decidua.

The factors that bring about the bleeding are considered to be the death of the fetus and hormonal changes associated with such death. The complete anatomic and the physiologic phenomena in the decidua that produce desquamation and bleeding have not been fully described. It is with this phase that the present work is concerned.

MATERIAL AND METHODS

In a series of more than 650 proved tubal pregnancies, it was necessary to remove the essentially normal uterine body in 16 instances. These uteri furnish the material for this study.† Traumatism of the uterus was avoided during abdominal hysterectomy by clamping the round ligaments. No instruments were applied to the uterus. There was no vaginal manipulation nor curettage of the decidua.

Each uterus after removal was opened and fixed either in 10 per cent neutral formalin or aqueous-formol-chrome-sublimate. The blocks of tissue taken were not larger than 10 by 5 by 3 mm. They all contained the entire thickness of the decidua and some myometrium. After embedding in paraffin, 7 μ sections were cut and arranged serially in each instance. The stains used were Mallory's connective tissue stain, hematoxylin and eosin, Bielschowsky-Maresch silver stain, and Best's carmine stain.

*Presented at the Sixty-Fourth Annual Meeting of the American Gynecological Society, White Sulphur Springs, W. Va., May 22 to 24, 1939.

Aided by the Albert B. Kuppenheimer Fund of St. Luke's Hospital, and a grant from Mrs. Emmons Blaine.

†Grateful acknowledgment is made to Dr. James E. Fitzgerald and Dr. George H. Gardner for a portion of these specimens.

DESCRIPTION OF SPECIMENS

The specimens described here in detail were chosen because they demonstrate most clearly the complete phenomena of uterine bleeding and slough.

CASE 1.—Mrs. H. G. (No. 14 in our series), aged 29 years, entered the hospital May 31, 1938. Her menses occurred regularly every twenty-eight days with a three- to five-day flow. The last normal menstrual period began April 3, 1938. On May 8, 1938, spotting began and continued through May 28, 1938. On May 29 and 30, the two days prior to operation, there was no bleeding. Cramping pain persisted from May 8 to the time of operation. At operation, May 31, 1938, the uterus was removed supracervically with the unruptured left tubal pregnancy.

The uterus after supracervical removal is 7.5 by 5.0 by 4.0 cm. Its surfaces are smooth and glistening. On surfaces made by cutting, the decidua is 7 to 8 mm. thick. The myometrium appears normal.

The left tube is 9 cm. long, and in its greatest dimension in the midportion is 4.5 cm. wide. The lumen is filled with clotted blood. In the dilated central portion there is a placental site of a tubal pregnancy.

The uterine cavity contains no blood. The decidua is in folds which are as thick as 6.8 mm. after fixation in formalin. The decidua is covered with surface epithelium. The decidua is differentiated into compact, spongy, and basal zones identical in arrangement to that in vera of normal intrauterine pregnancy. The compact zone is as thick as 4 mm. (Fig. 1). The stromal cells are differentiated into typical decidual cells of pregnancy. There is a small amount of intercellular edema fluid. The gland necks are far apart, elongated, and narrow. The gland cells are flattened. Large blood filled venous sinuses are located in the compact zone. Spiral arteries and their branches reach to the surface. The spongy zone (2 mm. thick) contains considerable edema (Fig. 1). The glands which comprise most of the spongy zone are the typical Opitz glands of pregnancy. The cells are columnar. Some glands contain secretion. The stromal cells are small. Traversing the spongy zone are numerous venous spaces and spiral arteries. Around these latter structures the stroma is condensed. The basal zone is characterized by a dense stroma and glands that evidence less secretory activity than those located in the spongy zone. Some glands extend downward into the myometrium.

CASE 2.—Mrs. L. C. (No. 6 in our series), aged 30 years, para ii, entered the hospital Jan. 13, 1936. Her menses occurred every twenty-eight days, lasting four to five days. Uterine bleeding began on Dec. 1, 1935, and lasted four days. The patient considered this a normal menstrual period. On Dec. 11, 1935, she began to spot and have cramping pains, both of which continued until the time of operation on Jan. 14, 1936.

At operation the body of the uterus and the right tube containing the pregnancy were removed abdominally. The tube in its midportion was distended to a maximum diameter of 4 cm. The uterus, 7 by 5 by 4 cm., was soft and congested. The tissues were fixed immediately in aqueous-formol-chrome-sublimate. The decidua of this specimen is in folds, similar to those in Specimen 14. It is as thick as 4.3 mm. In Fig. 2 the decidua at either end is 2.9 mm. thick. The midportion is thin. It measures 0.8 mm. The thick portions have a surface that is thrown into papillary folds and projections. The tips of the papillary projections are edematous and similar to those in Fig. 1. The compact zone is narrow (0.9 mm.). The decidual cell formation is meager. The blood-filled venous sinuses are quite superficial. There are occasional small superficial regions of extravasation. The gland necks are short (0.0424 mm.) and have low columnar and cuboidal cells that evidence no secretory activity. The spongy zone is 2.0 mm. thick. The glands are tortuous and the cells are columnar and filled with secretion. The stroma is dense and the cells are small. The basal zone is thin and is similar to that noted in Fig. 1.

The thin midportion of decidua (0.8 mm.) has sharp borders of differentiation from the adjacent region. The surface is flat. The surface epithelium is intact. The compact zone is narrow in contrast to that of the thick regions. There is no edema. The decidual cells are few, small, and crowded closely together. The

spiral arteries extend to the surface. The superficial capillary network is present. There is a slight extravasation of blood. Infiltration of leucocytes and lymphocytes is only occasional. The venous sinuses are not prominent. The gland necks are short and the cells are secretory in character. This is in direct contrast to the typical elongated gland necks with nonsecretory epithelium in the thicker regions of this specimen. The glands have extremely wide mouths. Some are as wide as 0.276 mm. In the adjacent thick portions the necks are 0.0424 mm. wide. In the spongy zone the glands are close together with only strands of stroma between them. The glands are wide in comparison to the glands in the thick regions. The glands in the former region are 0.339 mm. wide, while in the latter regions they are 0.127 mm. None of the cells of the glands in the thinned-out portion is as actively secreting as those in the thick regions. In this rather ill-defined spongy zone the venous structures are thinned and are not prominent. There is no edema. A basal zone cannot be differentiated.

Fig. 1.

Fig. 2.

Fig. 1.—Typical decidual reaction in the uterus in association with a seven weeks' tubal pregnancy. (Spec. 14.)

Fig. 2.—Midportion of the intact decidua is thin and compressed. At either end the intact decidua is thick and polypoid. (Spec. 6.)

In Fig. 3 the decidua is but 1.9 mm. thick. It is, therefore, thinner than many other regions in this uterus. It is not as thin as the low region described above (compare with Fig. 2). The zona compacta is markedly thinned. It contains little edema. The stroma cells are small and flattened and do not resemble true decidual cells. The gland necks are short and broad. In some regions there are small groups of leucocytes and lymphocytes just beneath the surface epithelium. A subepithelial hematoma of Gebhard is shown. The surface epithelium is stretched and flattened over this hematoma which is approximately 1.3 mm. in diameter. Venous sinuses are few and small.

The glands in the spongy zone show compression to a slight degree. They are secretory in character and resemble glands of pregnancy. There is some edema.

The venous structures are moderately dilated and contain blood. The stromal cells are small.

CASE 3.—Mrs. E. D., aged 30 years, entered the hospital June 14, 1934. Vaginal bleeding, spotting to moderate, began April 1, 1934 and continued up to the time of operation. Her last menstrual period was from Feb. 15 to Feb. 19, 1934. Associated with the vaginal bleeding there was a soreness in the right lower quadrant. A diagnosis of right tubal pregnancy was made and on June 16, 1934, the uterus, both tubes, and the right ovary were removed for a tubal pregnancy and residues of pelvic infection.

Fig. 3.—Subepithelial hematoma of Gebhard. The intact decidua is approximately one-half as thick here as in the remainder of this specimen. (Spec. 6.)

Fig. 4.—Region evidencing early desquamation is shown to be strictly localized. The arrow indicates a terminal portion of a spiral artery that has been sequestrated with a portion of decidua. This is shown at greater magnification in Fig. 21. The thicker intact portions of decidua have undergone partial involution as evidenced by the character of the glands.

Fibrous adhesions cover the uterus, both tubes, and the right ovary. The fundic portion of the uterus is 6 by 8 by 5 cm. The myometrium is 3.2 cm. thick. The right Fallopian tube has in its middle portion a circumference of 3 cm. It is filled with clotted blood. Adherent to the tube and the posterior surface of the uterus is a mass of clotted blood 10 by 9 by 2 cm. The decidua and a portion of the myometrium were fixed immediately in aqueous-formal-chrome-sublimate solution.

The cavity of the uterus studied under the dissecting microscope after fixation is lined with decidua that is arranged in folds and rugae similar to that found in

early pregnancy. The thick portions, which are 2.5 mm. thick, comprise 85 per cent of the total decidua (Fig. 4). The small isolated regions of low decidua (15 per cent) are 0.5 mm. thick (Fig. 5). Some of these thin regions have irregular, roughened surfaces to which blood clots, not exceeding 0.5 by 0.5 cm., are adherent (Fig. 4). Other thin regions have smooth regular surfaces (Fig. 5).

Fig. 5.—The decidua at the right is thick and edematous. At the left it is approximately one-half as thick and there is little edema. The surface epithelium is intact. A spiral artery of large caliber lies immediately beneath and parallel to the surface epithelium. This denotes the effects of compression, principally from the loss of edema in the involution phase before slough. Arterial spasm is noted in this vessel. (Spec. 3.)

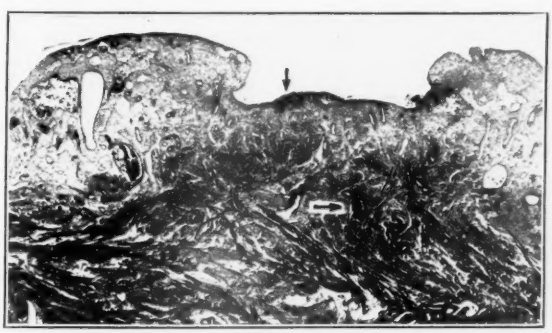

Fig. 6.—The decidual tissue at each end of this photomicrograph is thick, contains edema and large venous sinuses. Regression in the glands has occurred. The processes of involution have reduced the decidua by 50 per cent in the midportion. The surface epithelium is intact. No slough has occurred. The spiral artery that supplies this localized region is indicated by an arrow. The second arrow indicates superficial extravasation. (Spec. 3.)

In the microscopic sections the thicker portions of the decidua are imperfectly arranged into compact, spongy, and basal zones. The surface epithelium is intact (Figs. 5 and 6). The superficial zone which represents the compact zone is edematous and contains numerous large venous sinuses. Many of the venous spaces are filled with blood. There is no extravasation and little evidence of diapedesis. There are only a few lymphocytes and plasma cells scattered through the stroma. Spiral arteries course through the spongy zone with occasional branching to reach to the surface epithelium. A superficial capillary network is present at the termination of the spiral arteries and their branches. The gland necks are narrow and they

Fig. 7.—A three dimensional reconstructed model of the spiral artery supplying the portion of the decidua that evidences involution in Fig. 6. The myometrial-decidual junction and the surface epithelium are indicated. Branch (*Y*) is constricted through most of its course. Superficially it lies immediately subjacent to and parallel with the surface epithelium (see Fig. 13). Branch (*X*) is constricted basally and markedly dilated immediately beneath the surface (see Fig. 8). The constriction of branch (*Y*) is shown in Fig. 11 and that in branch (*X*) in Fig. 8. The surface epithelium is degenerated at the terminal portion of branch (*X*). These arteries represent true end arteries.

are shorter than those present in the decidua of a normal uterine pregnancy. The gland cells of the necks are large and cuboidal in contrast to the stretched-out epithelium which O'Leary (1929) described in early decidua vera. The stromal cells in the compacta are small, elongated, and have flattened nuclei. They do not resemble decidual cells.

In the poorly differentiated spongy zone there is moderate edema. The glands are infrequent. They are only slightly tortuous in shape. There is little secretion in their lumens. Glycogen is not stained in the gland cells after aqueous-formol-chrome-sublimate fixation. The glands do not resemble the glands of pregnancy. In this zone there are numerous large, blood-filled venous spaces. Many extend in

a vertical plane. The sinuses are most numerous and largest near the junction of the peripheral one-third and proximal two-thirds of the decidua.

The basal zone is differentiated only by the horizontal position of some of the glands and the fact that there is slightly less edema as compared to the spongy zone. The glands extend down into the myometrium for a short distance. All of these findings are shown best in Fig. 4. Large dilated venous sinuses in the myometrium are frequent (Fig. 4).

The thin portion of the decidua is in marked contrast to the thick region as shown in Fig. 5. The essential features that differentiate the two are the variations in amount of edema fluid and number and size of engorged venous sinuses. The borders of separation of the two regions are definite.

In the thin region (0.5 mm.) there is no separation of the decidua into zones such as described for pregnancy. The surface epithelium is intact. Throughout the decidua the stromal cells are elongated and small. They are equal in size and are packed closely together. They do not resemble decidual cells. There is no intercellular edema fluid. The glands are few in number, widely separated, and resemble those of a postmenstrual stage. They evidence no secretory activity. A spiral artery of large caliber reaches to the surface epithelium. Its course through the decidua is diagonal. Just beneath the surface it is bent laterally to lie parallel with the surface. The large loops just beneath the surface epithelium are dilated and contain little blood (Fig. 5). In this superficial region there is branching. There is a very meager capillary system at the terminal ends of this artery and its branches. In the myometrium just beneath the decidua, there is a constriction which, although not complete, is definite. The surface epithelium immediately over this large vessel is flattened in places. Some of the cells cannot be differentiated from adjacent stromal cells except by position and continuity with surface epithelium. Some cells evidence slight degenerative changes.

Fig. 6 is a photomicrograph of a section from a block of tissue taken from another portion of the same uterus, showing two thick regions (2.03 mm.) separated by a thin region (0.34 mm.). The localized thin region has a width of 2.9 mm. The thick regions are identical to those shown in Figs. 4 and 5.

The thin region, which is extremely low, has an intact surface epithelium (Fig. 6). This epithelium is flattened in numerous places. The flat epithelium is differentiated from the underlying stroma only by position and by continuity with adjoining surface epithelium. Occasional large surface epithelial cells, two to four times the usual size, are noted. The nuclei are large, irregular, and are stained poorly. Flat epithelial cells project over the edge of the cuboidal surface epithelium in places. The impression is obtained that this flattened epithelium is in the process of migrating over the surface. Many epithelial cells have irregular cell membranes and pyknotic nuclei. In this extremely low region of the decidua there is no differentiation into zones characteristic of pregnancy. In the superficial zone there are some regions of extravasation beneath the surface epithelium (Fig. 6, see arrow). These are located about the terminal ends of spiral arteries.

The stromal cells are compact, small, and spindle shaped. There is little edema. The glands are few, far apart, and resting stage in character. The cells in the gland necks are undergoing mitotic division. There are a few small venous spaces present. Scattered through the stroma are many leucocytes and lymphocytes.

The spiral artery located in the center of this involuted region (Fig. 6) is shown in a three dimensional reconstruction in Fig. 7. It approaches the decidua in a perpendicular fashion and divides into two main branches just before entering that structure. The larger branch (*X*) is but moderately coiled. It is constricted through most of its course through the decidua, and its lumen is empty. It branches once in the peripheral one-third of the decidua. The terminal portion of the arteriole is markedly dilated and is filled with blood (Figs. 7 and 8). Here extravasation is greatest (Fig. 8). The surface epithelium overlying this region is denuded and there is some small hemorrhage into the uterine cavity. Fig. 9 shows a portion of the tip of this branch, dilated and filled with blood. The endothelial wall is ruptured at one point and extravasation has occurred. In this region there are occasional capillaries found. In Fig. 10 extravasation about the tip of an unruptured terminal arteriole is shown. The surface epithelium is intact.

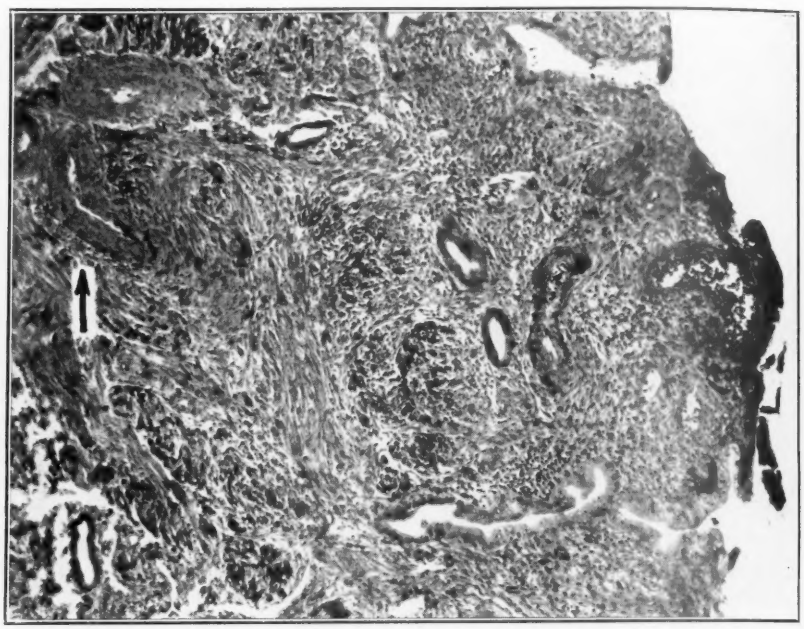

Fig. 8.—Showing the entire thickness of the decidua and a portion of the myometrium. Branch (*X*) of the artery shown in Fig. 7 is dilated superficially and constricted in the myometrium (arrow). Extravasation and necrosis are present at the tip of the artery (see Figs. 9 and 10).

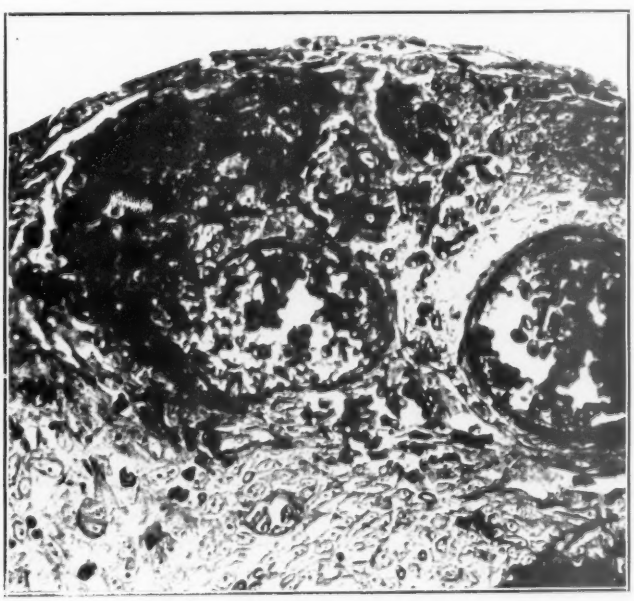

Fig. 9.—The tip of branch (*X*) shown in Figs. 7 and 8 has a defect in its wall with resulting extravasation by rhexis. The superficial epithelium is partially necrosed.

Branch (*Y*) is relatively straight and uncoiled. It is constricted and empty (Figs. 7 and 11). It reaches to the surface unbranched. The surface epithelium is undergoing degenerative changes in the region where the artery terminates. The stroma is disrupted. The arteriolar wall is unruptured and extravasation has occurred (Fig. 12). A few blood cells have entered the uterine cavity. Near the tip of this branch the artery has a thick muscle coat, lies parallel to and immediately beneath the intact epithelium (Figs. 7 and 13).

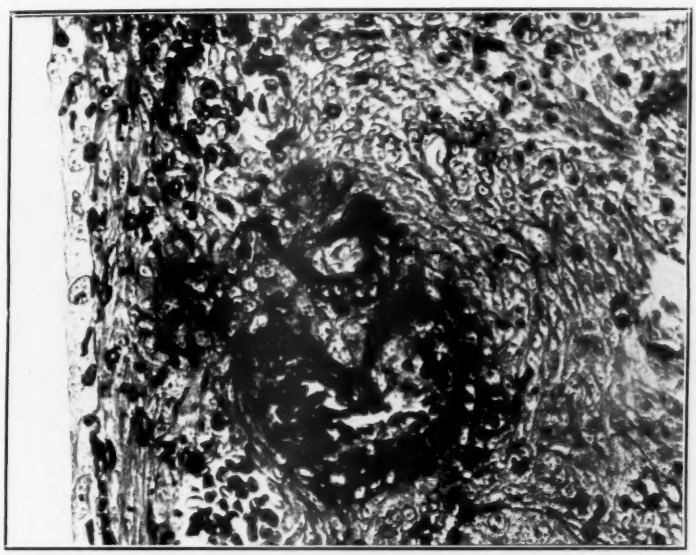

Fig. 10.—Tip of branch (*X*) (Fig. 7) with extravasation by diapedesis immediately beneath the intact surface epithelium.

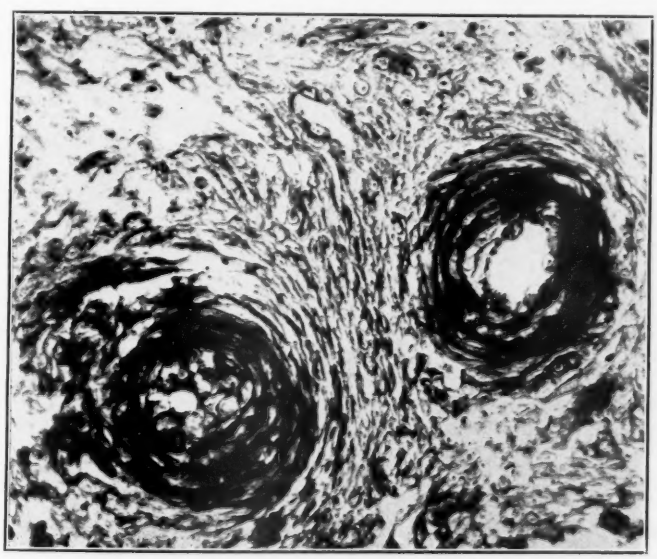

Fig. 11.—Cross sections of a loop of branch (*Y*) (Fig. 7) demonstrating marked constriction near the myometrial-decidual junction.

Figs. 4 and 14 are photomicrographs of sections from blocks of tissue that were taken from different portions of the same uterus. At either end of the sections the decidua averages 2.5 mm. while the low region is as thin as 0.5 mm. There is sharp differentiation between these regions. The thick portions are similar to the thick regions shown in Figs. 4 and 5. The glands evidence some slight secretory activity. The venous sinuses are numerous and contain blood.

The thin region of decidua has no intact surface epithelium except at the margins (Figs. 4 and 14). Where the covering epithelium is wanting, the decidual surface is very irregular. Glands, vessels, and stromal cells jut unevenly into the uterine

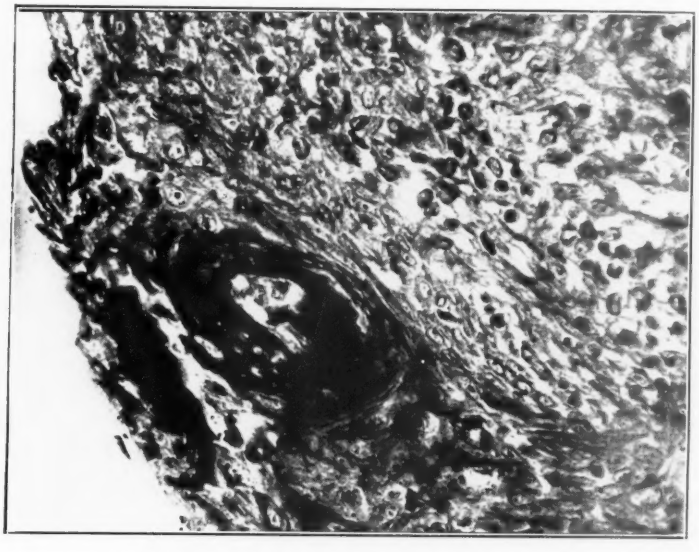

Fig. 12.—Extravasation and partial necrosis of the surface epithelium at the termination of the arterial branch (*Y*) (Fig. 7).

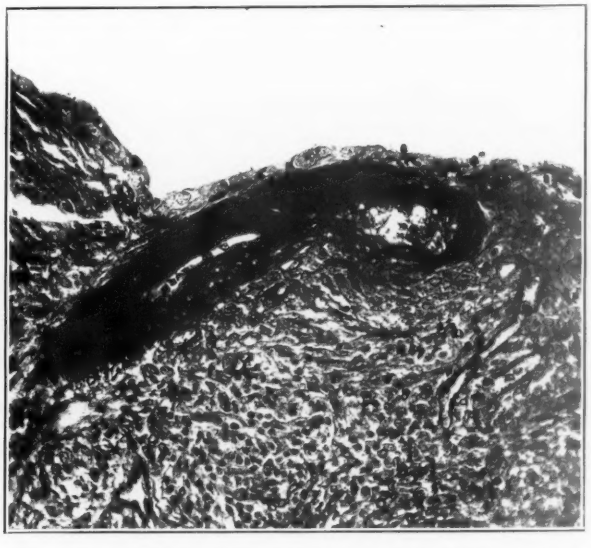

Fig. 13.—Intact surface epithelium overlying the horizontally placed large arterial branch (*Y*) near its termination (see Fig. 7).

cavity. Blood cells, fragments of tissue, individual endometrial stromal cells, some surface epithelium, and precipitated fluid are located free in the uterine cavity just above these surfaces (Fig. 4). Many of the cells appear normal while others are definitely degenerated. In this region the thickness of the decidua is the same

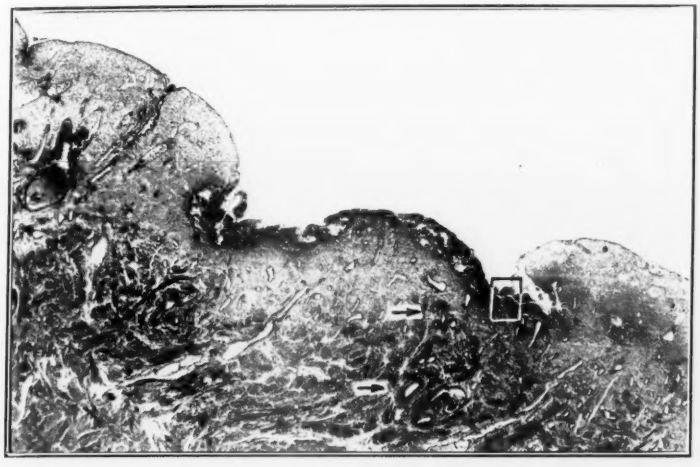

Fig. 14.—Characteristic localized region of superficial desquamation. The large artery that alone supplies this region is indicated by arrows. Extravasation is marked. (Spec. 3.)

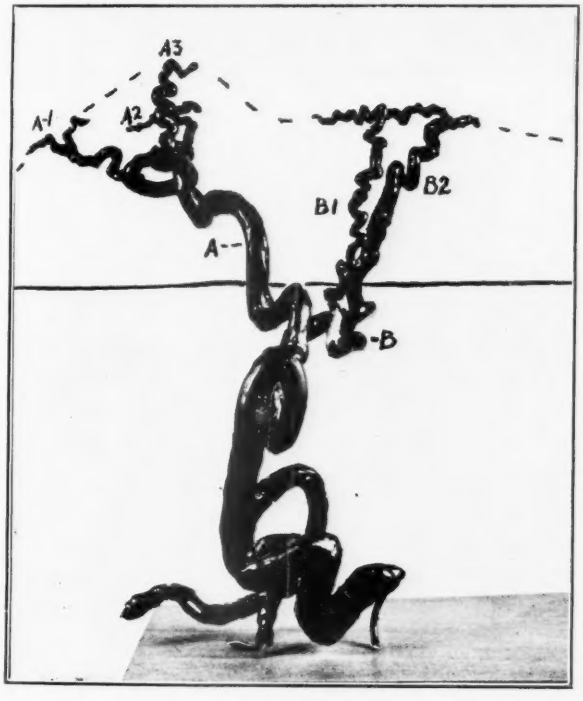

Fig. 15.—A three dimensional model of the end artery shown in Fig. 14 reconstructed from serial microscopic sections. The myometrial-decidual junction and the surface of the decidua are indicated. Each of the two main endometrial branches evidences physiologic constriction (see Figs. 16 and 19).

as in the marginal regions where the surface epithelium is intact. This clearly demonstrates that as yet there has been little actual loss of tissue. These facts indicate this to be an instance of beginning desquamation. In the peripheral part of the decidua numerous small masses or flakes of "elastoidin" are found. They are located close to the vascular structures.

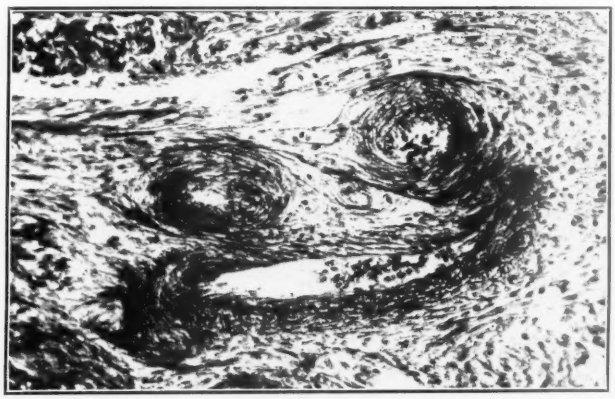

Fig. 16.—Cross and longitudinal sections of a spiral artery loop in branch (*A*) demonstrates constriction. The location of this constricted portion is indicated by an arrow in Fig. 14.

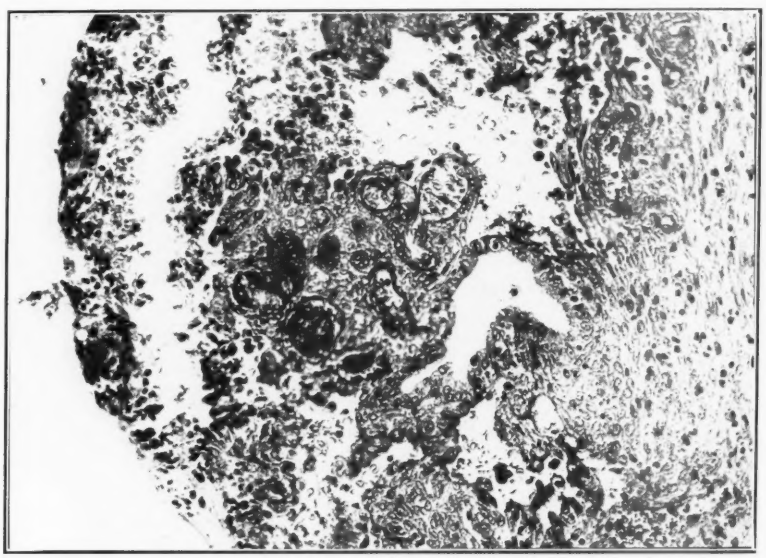

Fig. 17.—The terminal portion of a branch of the endometrial artery branch (*A*) (see Fig. 15) with its dilated lumen filled with fibrin.

The artery that is located in the center of the sloughing region in Fig. 14 projects toward the decidua in a perpendicular plane. Just before entering the decidua the vessel divides into two main branches (Fig. 15). Each enters the decidua in a slightly oblique manner. The larger branch (*A* in Fig. 15) is constricted over a short distance in the myometrium just beneath the decidua (Fig. 16). It has few coils in the proximal one-half of the decidua (Fig. 15). In the peripheral half, however, the coils are numerous and tight. Throughout the decidua this branch has little blood in its lumen. The artery divides into three branches in the peripheral decidua. Each branch extends to the irregular desquamating surface.

About the terminal ends of each, extravasation has occurred. Fig. 17 shows the tip of branch (*A*, *1*). It is slightly dilated and is filled with blood. It is located in a fragment of desquamating decidual tissue where it is occluded. There is considerable blood in the uterine cavity and in the disrupted stroma in this region.

Fig. 18.—Superficial decidual tissues showing extravasation, disintegration, and slough. The artery supplying this region has a defect in the wall near its termination, through which extravasation by rhexis occurred (arrow). The constriction in this artery that produced the ischemic necrosis and the resulting break in the arterial wall is shown in Fig. 16. (Spec. 3.)

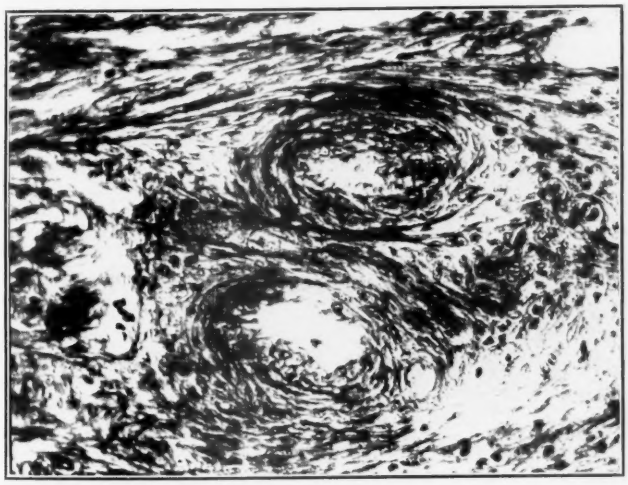

Fig. 19.—The loop of the spiral artery (branch [*B*], Fig. 15) evidences constriction.

The endothelial cells have irregular cell membranes and the nuclei in many instances are pyknotic. There is no demonstrable capillary network here.

Fig. 18 shows the tip of branch (*A*, *2*) (Fig. 15). The slightly dilated terminal arteriole has a defect in its wall at one point. The adjacent endothelium is undergoing degenerative changes. Through this defect extravasation has occurred. Blood fills the disintegrating decidual tissues and some is located in the uterine cavity. There is no capillary network.

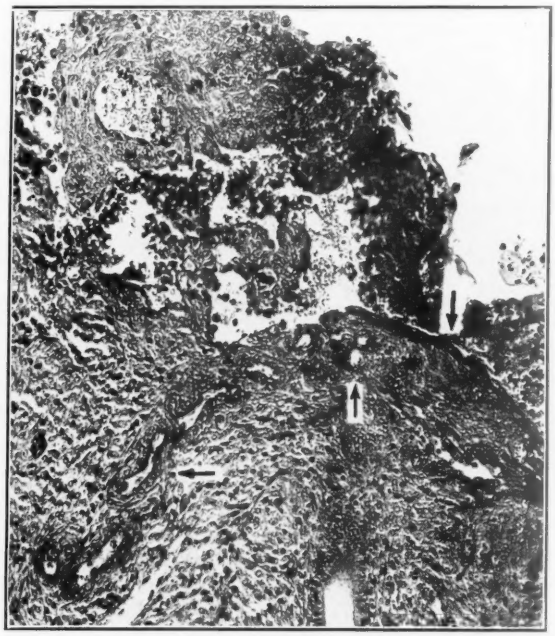

Fig. 20.—Superficial half of a region of decidua, part of which on the left is desquamated, and part on the right that is still covered with surface epithelium. The blocked zone in Fig. 14 indicates this region. A spiral arterial branch with an empty lumen extends laterally beneath the intact surface epithelium. This is indicated by arrows.

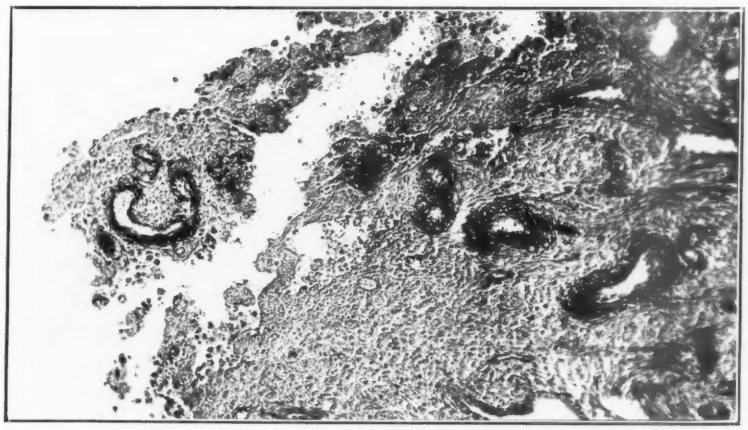

Fig. 21.—Terminal portion of an artery (branch [*B*], Fig. 15) sequestrated with a portion of decidua (see Fig. 4). There is no blood in its patent lumen and there is no hemorrhage about its tip. The constriction in this vessel is shown in Fig. 19.

The terminal portion of branch (*A, 3*) has extravasation about it. No capillary network is evident. The minute arteriolar branches, of which there are several, are not involved in the desquamation to the extent observed in branches (*A, 1*) and (*A, 2*). The tips of each are patent but no great hemorrhage has occurred.

Branch (*B*) (Fig. 15) is constricted also in the myometrium just beneath the decidua. The constriction is definite (Fig. 19). The vessel as it courses through the decidua contains little blood. At the myometrial-decidual junction a small branch is given off that extends to the surface (branch *B, 1*, Figs. 15 and 20).

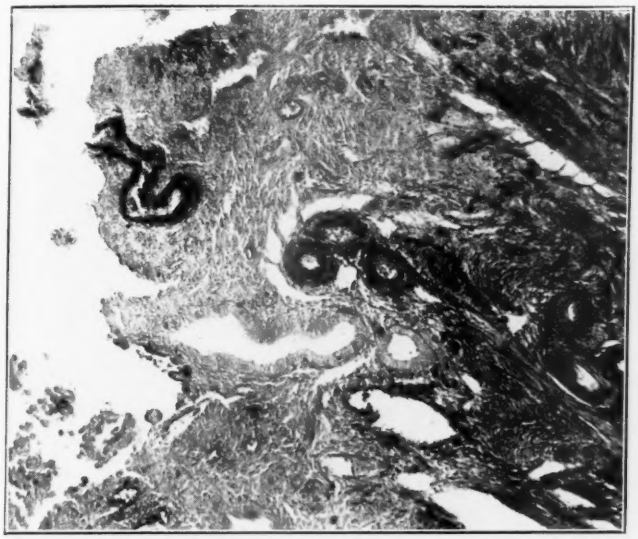

Fig. 22.—The partially desquamated decidua with a portion of myometrium is shown. The spiral artery with its empty lumen juts free into the uterine cavity. There is no hemorrhage about its tip. The constriction in this artery is shown in Fig. 23.

Fig. 23.—Physiologic constriction in the artery shown in Fig. 22.

This branch is constricted through most of its course and contains little blood. It bends laterally just beneath the surface (Fig. 20). Here the surface epithelium is intact. The branch is everywhere intact and its lumen patent. No capillary network is present.

The larger branch (*B, 2*) is tightly coiled. Near the surface it divides into several smaller branches. One branch is in the process of being desquamated with a bit of decidual tissue (Figs. 4 and 21). While extravasation is abundant here, there is no marked hemorrhage although the lumen is patent. One terminal branch lies parallel to the sloughing surface. Portions of the vessel are involved in the desquamation, its lumen is patent, yet no hemorrhage is evident. No capillary network is present.

In another block of tissue from the same uterus the findings are similar to those described above. The thicker portion of the decidua is 1.4 mm. thick. It is covered with surface epithelium. The decidua is not divisible into layers or zones. There is little edema in any region. The stroma cells are homogeneously distributed. They are spindle shaped and do not resemble decidual cells. The venous sinuses are not as large or as numerous as in other blocks of tissue described above. Spiral arteries reach to the surface. The glands are few, far apart, and are only moderately active in secretory character.

The thin portion has a maximum thickness of 0.9 mm. This portion resembles in all details that shown in Figs. 4 and 14. In Fig. 22 a large artery is shown projecting free into the uterine cavity. Its lumen is patent. There is little blood in its lumen. There is no hemorrhage about its open end. Serial reconstructions demonstrate a localized constriction of its lumen near the myometrial-decidual junction (Fig. 23).

DISCUSSION

In instances of tubal pregnancy it is a well-known fact that the endometrium develops into typical decidua (Fig. 1). The extent of development depends upon a continued growth of the fetal trophoblast, uninterrupted corpus luteum stimulation, and continued pituitary hormonal secretion. Certain alterations in any one of these, each dependent upon the other, bring about regression of the decidua with associated uterine bleeding.

The first phase of the process of uterine bleeding is involution. In describing normal menstruation, Bartelmez (1931) stated that this phase had been neglected recently by most authors. He demonstrated (1931) that involution reduced the thickness of the endometrium by 50 to 60 per cent before slough and bleeding occurred. He showed (1933) that involution was brought about principally by four factors: (1) a disappearance of edema, (2) a loss of secretion from the glands, (3) a diminution of the blood supply, and (4) a diminution in size of the gland and stroma cells.

A distinct advantage in the study of involution in our material is had in the fact that in many instances one section properly chosen shows small regions of involution or slough bounded on all sides by decidua that has been less involved (Figs. 2, 4, 5, 6, and 14). These small isolated regions of involution and slough are comparable to similar localized regions in the endometrium in normal menstruation. Bartelmez (1933) stressed that menstruation in the human being may involve but small local regions at a time and that only gradually the entire mucosa becomes involved in the phenomenon.

The loss of edema fluid which usually occurs first in the process of involution is shown in Figs. 2 and 5. The decidua has been reduced in

thickness in a definitely localized region from 3.5 to 1.0 mm. as compared with the adjacent normal decidua in Fig. 2. The glands are markedly compressed. They are in a typical secretory phase and the cells are not decreased in size. The compact stroma is compressed without decrease in size of the individual cells. Compression of the glands is indicated first, by decreased length, second, by increased width in many instances so great that the glands are adjacent with little intervening stroma, third, by marked widening of the gland mouths, and fourth, by absence of gland necks. The spiral arteries that reach to the surface terminate in capillary networks. Slight extravasation has occurred. The venous spaces have disappeared. The leucocytic, lymphocytic and plasma cell infiltration, stated by Novak and TeLinde (1924) to occur prior to menstruation, is evident here. That these regions have been thicker and have become thinned is suggested by the above facts and in addition is proved by a study of the arteries. The arteries here are much larger in comparison to the thickness of the decidua (Fig. 5). The large caliber of the vessels immediately beneath the surface epithelium demonstrates that the decidua has become thinner. Thus, in this particular locality the beginning of involution is characterized primarily by a reduction in thickness of the decidua due to a loss of edema fluid.

In another specimen, however, involution has been initiated by a regression of the glands. They are not secretory in type but resemble a resting stage (Fig. 4, thicker portion of decidua). The cells are reduced in size and glycogen is not stained following aqueous-formol-chrome-sublimate fixation. That these glands were previously fully developed and secretory in character and have regressed is evidenced by the fact that all the other elements of the decidua denote complete corpus luteum stimulation. These are namely, the development of venous sinuses, spiral arteries reaching to the surface, a superficial capillary network, and marked edema. It does not seem probable that all these evidences of stimulation could be present without some associated stimulation of the glands. Here there has been little apparent loss of edema fluid and consequently little reduction in the thickness of the decidua. There is no extravasation, rhexis, or slough evident in this region. It is conceivable that even under normal conditions such as menstruation, involution may be heralded in by any one of the different features that characterize it. Bartelmez (1933) has indicated this to be true. This specimen also demonstrates small thin regions in which the glands have regressed as noted above and in addition there has been a loss of edema fluid which accounts for its thinness. That this is a regression phenomenon is conclusively demonstrated by the fact that large spiral artery loops reach to the surface (Figs. 4, 5, 8, and 13) in contrast to the normal position and caliber of such vessels.

The third factor in involution, extravasation and a diminution of the blood supply, is demonstrated in Fig. 3. A subepithelial hematoma of Gebhard which results from a rupture of the superficial capillary bed is shown. Similar hematoma formations are constant features of normal menstruation. Preceding this rupture and hematoma formation, there has been a loss of edema fluid as evidenced by the compactness of the

stroma and by the fact that the decidua here is 1.9 mm. thick, whereas the regions that still retain edema are as thick as 3.8 mm. This is similar to normal menstruation in which Bartelmez (1933) states that loss of edema usually precedes extravasation and hematoma formation. Extravasation in the superficial portions of the decidua which evidence involution is a constant finding here (Figs. 6, 8, 9, 10, and 12) as it is in menstruation.

When involution has progressed further, pictures such as Fig. 4 are observed. In the midpoint the decidua is approximately 50 per cent as thick as the adjacent, surrounding less involved tissues. All the edema fluid has been lost. The glands have ceased their secretory activity and are typical of a resting stage. The gland and stroma cells are reduced in size. In addition there has been a reduction in circulation since the superficial capillary bed is absent. The terminal arterioles have in many places endothelial cells with pyknotic nuclei and some have defects in their walls. Through these defects blood escapes into the surrounding tissue (Figs. 9 and 18). Thus, about the terminal vessels extravasation is noted. In some instances (Fig. 10) the surface epithelium is intact over these vessels. In others, the surface epithelium is absent only over the terminal tip of the vessel (Figs. 8 and 12).

In conjunction with the reduced flow, disruption of the capillary bed, and extravasation, there is a necrosis of the surface epithelium in this specimen (Fig. 4). The necrosis in places has proceeded far enough so that the surface epithelium is destroyed. Involved in this is a degeneration of the stroma cells. A disruption of the stroma framework results from the reduced circulation, the distention of the extravasated blood, and the presence in the locality of leucocytes and lymphocytes. Bartelmez (1933) described this for menstruation. This whole phenomenon then results in a desquamation and disintegration of the superficial decidual structures. The tissue separates and is cast off in fragments and individual cells (Fig. 21) as Novak and TeLinde (1924) and Bartelmez (1931 and 1933) have described for menstruation. The slough involves the terminal ends of arterioles (Figs. 17, 18, 21, and 22), veins, stroma, surface epithelium, and glands.

In some instances the sloughing process occurs in such a way that arteries jut free into the uterine cavity (Figs. 21 and 22). Here there is no clot in the lumen and there is no hemorrhage about it. The absence of blood in these vessels, the absence of clots in the lumen, and the absence of hemorrhage about the tips suggest vascular control for these phenomena.

ARTERIAL SYSTEM

The study of the spiral arteries in the decidua of the specimens reported here shows that they are located every 4 to 8 square millimeters. A similar spacing of these vessels was noted in normal human menstruating uteri by Bartelmez (1933). The arteries branch in the superficial one-third of the decidua and terminate near the surface in capillary networks.

It has been demonstrated that each small localized region of decidua that is involved in early involution, disintegration, and slough in these specimens is that which is supplied by a single spiral artery and its branches (Figs. 5, 6, and 14).

This immediately indicates the importance of the spiral artery. There are many such localized regions scattered throughout the decidua. As these processes, typical of menstruation continue, the number of small localized regions increase, coalesce, and as a result, larger portions of the decidua become involved.

The importance of the spiral arteries in normal menstruation has been demonstrated by Bartelmez (1933), Markee (1933 and 1936), and Daron (1936). Bartelmez (1933) confirmed the suggestion that the processes of involution, disintegration, and slough were the result of ischemic necrosis. He demonstrated that ischemic necrosis resulted from physiologic vascular constriction. The vascular constriction frequently occurs in the spiral arteries in the myometrium just beneath the endometrium. Markee (1933 and 1936) in studying endometrial transplants in the anterior chamber of the eye in the macaque observed that individual arterial constriction might endure for as long as forty-eight hours. During this period the superficial portion of endometrium supplied by the particular artery in spasm became ischemic and appeared white. With relaxation of the spasm, the renewed circulation burst through the terminal capillary system and produced the superficial hematoma of Gebhard. As the time of menstruation approached, the periods of constriction greatly predominated over the periods of relaxation. Markee concluded that the reduced circulation accounted for the superficial necrosis of the endothelium, stroma, superficial epithelium and glands which eventuated in menstrual disintegration and slough. Daron (1936) demonstrated that the basal zone of the endometrium is supplied by an arterial system which is separate from the arterial system that supplies the remainder of the endometrium. These arteries, he showed, did not manifest the profound physiologic vascular constriction noted in the larger spiral arteries. In this manner he explained the absence of necrosis of the basal zone in menstruation.

In the specimens of this report, physiologic vascular constriction and the resulting phenomena are identical to those phenomena observed in normal menstruation as described above. That physiologic vascular constriction does occur is demonstrated in Figs. 7, 8, 11, 16, 19, 20, 21, 22, and 23. This phenomenon is found in the spiral arteries supplying the localized zones of involution, extravasation, and slough. Figs. 5, 6, and 14 show the relation of these vessels to their localized zones.

The results of such physiologic vascular constriction are, first, involution. The process of involution is usually initiated by the loss of edema fluid as noted above. Figs. 2, 5, and 6 show regions in which edema fluid has been lost without slough and with intact surface epithelium. The constrictions in the spiral arteries supplying these regions are shown in Figs. 5, 7, 8, and 11. The small localized regions of involvement in these specimens are supplied by a single spiral artery as noted above. That such an artery is an end artery is evidenced by the fact that constriction of the main vessel or large branch produces an ischemic necrosis of all the tissues supplied by this vessel or branch. Apparently any collateral circulation that may be present is not adequate to prevent necrosis of the tissues supplied by these end arteries.

In these thin regions undergoing involution extravasation is more marked than in the thicker adjacent region (Figs. 3, 6, 8, 9, 10, and 12.) It is in the thin, involuting region that vascular constriction is noted. The extravasation occurs at or near the terminal ends of the spiral arteries and their associated capillary networks (Figs. 6, 8, and 10). One artery of large caliber is shown in Fig. 13 to lie horizontally to and immediately beneath the intact surface epithelium, which indicates the compression resulting from thinning of the decidua in this region. In serial sections approximately 1 mm. distant, the terminal end of this artery is found. It lies near the surface, and about it there is marked extravasation. The surface epithelium immediately overlying it, and here only, is partially disrupted. The constriction in this particular vessel is shown in Fig. 11. Fig. 5 also demonstrates in another portion of the same uterus arterial compression and lateral deviation associated with involution prior to slough. Constriction is noted in this vessel also.

Continued vascular constriction results in disintegration and slough of the superficial decidual tissues in regions of involution as described above. Fig. 8 demonstrates the earliest phase of slough observed in the specimens reported here. The

slough involves at first only the tissue lying immediately above the dilated terminal branch of an artery which is constricted throughout most of its course in the decidua (Figs. 7, 8, 11, and 12). The vessel wall is everywhere intact. In later stages of slough (Figs. 4, 14, 17, and 18) the loss of tissue is greater and extravasation is more marked. The artery that supplies this region evidences constriction near the myometrial-endometrial junction (Figs. 16 and 19). The ischemic necrosis that results from such constriction is indicated not only by the loss of tissue but also by a disruption of the endothelial wall in a terminal branch of this artery (Fig. 18). Thus, extravasation by rhexis is demonstrated.

In those thin regions in which slough is more extensive, the terminal branches of the arteries are involved in this process. Figs. 4 and 21 show a terminal portion of an arterial branch cast off into the uterine cavity in conjunction with decidual tissue. There is little extravasation and no hemorrhage about the open tip of this vessel. The patent and empty lumen indicates constriction and this phenomenon is shown in Fig. 19. Figs. 22 and 23 also demonstrate this phenomenon in its entirety. These phenomena indicate that during the phase of slough arterial structures are involved in the slough and that bleeding from these arteries is directly controlled by physiologic vascular constriction. In some instances in these specimens masses of fibrin fill the dilated terminal arterioles (Fig. 17). This may, in part, control the loss of blood.

We believe that the evidence presented indicates that arterial constriction accounts for the superficial extravasation, involution, disintegration, and slough that eventuate in uterine bleeding in tubal pregnancy in a manner identical to that demonstrated in menstruation by Bartelmez (1931 and 1933) and Markee (1933 and 1936). Furthermore, arterial hemorrhage during the phase of slough is probably controlled by physiologic vascular constriction.

CONCLUSIONS

1. The external bleeding present in most instances of tubal pregnancy is uterine in origin and is essentially a reflux venous flow.

2. The bleeding is associated with involution and desquamation of the uterine decidua.

3. In the early phases, the portions of the decidua so involved are small and are limited to the tissues supplied by a single spiral artery and its branches.

4. These arteries are true end arteries.

5. Involution, which results from constriction in the spiral arteries, may reduce the thickness of the decidua by approximately 50 per cent before slough occurs.

6. Marked superficial extravasation and the diffuse infiltration of leucocytes and lymphocytes occur during the involution phase.

7. The necrosis and disintegration of the superficial decidual tissues results from the ischemia produced by physiologic vascular constriction.

8. The terminal portions of spiral arteries that are involved in the sequestration of the decidual tissues do not evidence any extensive hemorrhage as a consequence of the physiologic vascular constriction in these arteries.

9. The phenomena of involution, extravasation, superficial ischemic necrosis with disintegration and desquamation, the absence of arterial hemorrhage, and the demonstration of physiologic vascular constriction described here are similar to the findings in normal menstruation.

REFERENCES

Bartelmez, G. W.: Am. J. Obst. & Gynec. **21**: 623, 1931. *Idem:* Contrib. to Embry., 142. Reprinted from Pub. No. 443 of Carnegie Instit. of Wash., p. 141,

1933. *Daron, G. H.:* Am. J. Anat. **58:** 349, 1936. *Fitzgerald, James E., and Brewer, John I.:* Am. J. Obst. & Gynec. **30:** 264, 1935. *Markee, J. E.:* Anat. Rec. (Supplement) **55:** 66, 1933. *Idem:* Ibid. **64:** 32, 1936. *Novak, E., and TeLinde, R. W.:* J. A. M. A. **83:** 900, 1924. *O'Leary, James L.:* Am. J. Anat. **43:** 289, 1929. *Sampson, John A.:* Surg. Gynec. Obst. **18:** 587, 1914.

104 South Michigan Avenue

DISCUSSION

DR. OTTO H. SCHWARZ, St. Louis, Mo.—The work of Jones and his associates shows beyond question that the changes that occur in the endometrium in the cases of uterine bleeding of extrauterine pregnancy are similar to those occurring in the endometrium at the onset of normal menstruation. Clinically we have always regarded the onset of continued uterine bleeding in extrauterine pregnancy as a sign of the disturbance of the pregnancy.

The most striking change that has been demonstrated by Jones takes place in the spiral arteries which, in my opinion, are entirely similar to those occurring in the normal endometrium at the onset of menstruation, as described by Bartelmez, Markee, and others, which the author has referred to. The underlying change preceding menstruation, irrespective of the causes, is the constriction of the spiral arteries. What causes them to constrict? I feel most likely that in the normal cycle it is the diminution of progesterone.

We all know theelin has a stimulating effect on smooth muscles and that progesterone has a relaxing effect. In pregnancy I believe that this relaxing effect has much to do with increasing the caliber of the uterine vessels, especially in the early months. This thought has led me to suggest that in cases of clear-cut pre-eclampsia the hypertension arising gradually may be caused by the withdrawal of the progesterone. We know in these cases that there is a constriction of the arterial loop of the capillaries of the nail bed with dilatation of the venous loop. In case of pre-eclampsia and eclampsia, we have always looked for some pressor substance to explain this phenomenon. It is interesting to mention here that Corner yesterday stated that some pressor substances have also been looked for as the cause of the constriction of the spiral arteries in the phenomenon of menstruation, and also without avail. Could not the deprivation of progesterone be the most important factor? Low pregnandiol figures have been reported for pre-eclampsia and especially eclampsia. With these thoughts in mind we are going to use progesterone in clear-cut cases of pre-eclampsia.

DR. RICHARD W. TE LINDE, Baltimore, Md.—Jones has shown in a very clear fashion the similarity between the mechanism of bleeding from the endometrium of the decidua of an ectopic pregnancy and from the menstruating endometrium. The changes in the endometrium associated with early pregnancy, extra- or intrauterine, and those in the late premenstrual period are subject to rather wide variations, wider, I believe, than are generally appreciated. It has always amused me to hear men speak of an eighteen-day endometrium and a twenty-one-day endometrium as though they could look through the microscope and tell from looking at the endometrium the exact day of the cycle. I do not believe that it can be done quite that accurately.

Some years ago I made a careful histologic study of the endometria of very early pregnancies and compared them with some late premenstrual endometria in which no pregnancy existed. In some cases, the endometria had more of the characteristic changes of early pregnancy in the late premenstrual nonpregnant cases than in some of the early pregnancies. For example, in the case of the Miller ovum obtained on the twenty-third day of the menstrual cycle, there was less glandular change, which we consider characteristic of pregnancy, than in some nonpregnant endometria at that same stage of the cycle and no decidualike change in the stroma cells except in the proximity of the embedded ovum. This stroma change only near the ovum makes me wonder whether the chorionic tissue does not have some power to generate progesterone even at this early stage instead of taking over the function at the seventieth to ninetieth day, as suggested by Browne. I would like to know whether Corner has observed this in monkeys.

We have always taught that if one suspects an ectopic pregnancy, and a curettage is done and the endometrium is found to look pretty definitely like early decidua, without chorionic villi, one can be sure that an extrauterine pregnancy exists. Perhaps we should modify our concept somewhat. I now have three cases in which the endometrium looked quite typical of early pregnancy, there being very definite decidualike change in the endometrium without chorionic villi, and no tubal pregnancy existed. In fact, one girl had had a previous bilateral salpingectomy. In one case in which the Friedman test was positive only a corpus luteum cyst was found at operation. Apparently, then, there is some variation in the response of the endometrium to the progesterone or possibly, as is suggested by Browne's pregnandiol determinations, some variation in the amount of progesterone which is produced in pregnancy, whether intra- or extrauterine.

Just as there is a variation in the endometrial build-up, so is there a variation in the method of casting off the early decidua. The way described by Jones is undoubtedly the usual one but just as we occasionally see membranous dysmenorrhea we see, now and then, an entire endometrial cast come away from the uterus. The sequence of events is: Tubal rupture, death of the fetus, degeneration of the corpus luteum, withdrawal of progesterone, and finally shedding of the decidua.

Now my last point: Is the endometrium the only source of vaginal bleeding in tubal pregnancy? Jones said he thought the endometrial bleeding was the usual cause but I think I have one case which definitely proves it is not the only method. In order to have it we must assume death of the fetus and shedding of the endometrium. Some time ago I operated upon a ruptured tubal pregnancy of four months' duration in which there was vaginal bleeding. The fetus was definitely alive and I believe the bleeding must have come through the tube and through the uterus into the vagina, and not from the endometrium.

DR. J. C. LITZENBERG, MINNEAPOLIS, MINN.—As you will remember, the older writers on this subject thought that the bleeding came from the site of the implantation of the ovum in the tube. Sampson has proved that the bleeding from an ectopic pregnancy was chiefly from the uterus and not from the tubes.

In 1920 I confirmed the findings of Sampson with further evidence. There was no blood in most specimens of tubes except for a very few millimeters, between the implantation of the tube and the uterus. I was unable to find any evidence of blood coming from the site of the implantation. In a case of interstitial pregnancy studied by serial section and reported before this Society, there was no blood coming from the implantation site, and absolutely no blood in the tubes toward the uterus. Jones has gone several steps farther and has told us just where the blood comes from, and why.

DR. GEORGE W. CORNER, ROCHESTER, N. Y.—It is most interesting to see that bleeding from the uterus in tubal pregnancy in its anatomic features closely resembles that of normal menstruation. This fact can be correlated very plausibly with the hormone-deprivation hypothesis of menstruation, discussed in my address of yesterday, because (as we may suppose) while the implanting ovum is struggling for a hold in the unfavorable environment of the Fallopian tube, the output of gonadotropic substance from the chorion is inadequate or inconstant and the production of ovarian hormones is disturbed. The uterine bleeding of ectopic pregnancy may well, therefore, be hormone-deprivation bleeding.

The conjecture of Schwarz that the direct cause of the bleeding is contraction of the uterine muscle is difficult to reconcile with experiments of Markee, in which estrin-deprivation bleeding occurred in endometrial grafts in the anterior chamber of the eye. In these grafts little or no uterine muscle is present. The vascular disturbance must therefore be located in the endometrial arteries.

I am glad that Schwarz has suggested trial of progesterone in the pre-eclamptic state. No one would be happier than I if progesterone were found to cure any one, of any disease. An experiment of this sort, interpreted as encouraging, was made in Edinburgh and reported about two years ago by Dr. Suzanne Paterson. Others who try this therapy should use large doses of progesterone.

The amount of ovarian hormones acting upon the endometrium is the end result of a complicated set of chain reactions, especially under the disordered conditions of an ectopic implantation. Normal responses of the uterus in the cycle or in pregnancy require a very critical balance between the ovarian hormones. It seems no wonder that their effects are variable when they are disturbed.

DR. OTTO H. SCHWARZ, ST. LOUIS, MO.—The activities of the nail bed are similar to the capillaries. The capillaries shown by Jones possess smooth muscle, but, irrespective of that, the corpus luteum may act on the vessels. It would be well to supplement any progesterone treatment with a study of the capillaries.

DR. EMIL NOVAK, BALTIMORE, MD.—In this discussion there has been repeated reference to the analogy which exists between the endometrial desquamation of tubal pregnancy and that of normal menstruation. While this may be granted, one may properly compare it also with the casting off of the decidua at parturition. I mention this because the material presented by Jones is difficult to interpret unless one knows the status of the tubal gestation in the reported cases. Is the pregnancy still progressing, or has the embryo long since succumbed? In the latter case, for example, the menstrual cycle can again be resumed, so that the blood vessel changes are those of the cycle, and they cannot be considered characteristic of tubal pregnancy.

The fact that blood vessels open directly on the surface during menstruation has long been known, but the more characteristic changes, according to the work of Markee and others, involve the more deeply placed spiral arterioles, and we know little as yet concerning the histologic changes concerned and the nature of the endocrine control of these blood vessels. Important though involution may be in association with endometrial desquamation, I do not believe it is quite as constant as many believe. If we study the tissue thrown off at menstruation, we frequently find considerable masses which still show large scalloped glands and a stroma characterized by granular degeneration rather than involution. The same observation may be made in the study of the large uterine casts which are at times thrown off after the death of the embryo in cases of tubal gestation.

DR. HAROLD O. JONES (closing).—All the details obtainable, including the measurements and the clinical evidence as to the death of the fetus, together with all factors that we thought pertained to this subject, are given in the published work. Time would not permit bringing those details to your attention.

I think we missed some of Sampson's work when he demonstrated before this Society the inability to inject the vascular bed during menstruation. Recent studies now being carried on by Bartelmez show that he is unable to get perfect delineation of the spiral capillaries in the menstruating endometrium.

We know that the decidua in the uterus of tubal pregnancy does present a very unusual pattern, and we agree that the factors that control these variations have to do with the reactions in fetal death. We have no way of determining that definitely, but we have contributed in our published article all the information that we could possibly get on that problem.

THE OVARIAN HORMONES AND EXPERIMENTAL MENSTRUATION*

GEORGE W. CORNER, M.D., ROCHESTER, N. Y.
(From the Department of Anatomy, the University of Rochester, School of Medicine and Dentistry)

OUR mastery of the ovarian hormones and knowledge of the physiology of menstruation have reached a point at which the menstrual cycle can be successfully imitated, in a castrate monkey or human female, with no other armament than a syringe and an ampoule of estrone. By merely timing, in a suitable manner, the course of estrone treatment to give a monthly cycle of estrone deprivation, a cycle of vaginal bleeding will occur, not externally distinguishable from natural menstruation. If any critical witness objects that this bleeding cannot be true menstruation, because the endometrium from which it proceeds has not undergone the so-called "premenstrual" changes, we may ask him to await the conclusion of this discourse before forming a judgment. Meanwhile we can satisfy his requirement by incorporating in our experiment suitably timed courses of progesterone, thus producing cyclically the premenstrual state and then in sequence the menstrual breakdown. Admittedly this refinement of the experiment is difficult to achieve in practice; effective balancing of the two hormones is critical and the histologic result not always perfect, but it will be agreed at least that we possess the means of producing, by the ovarian hormones alone, specimens exhibiting menstruation-like bleeding from the premenstrual endometrium. Having progressed thus far, the next step is to consider to what extent these experimental facts can be applied in explaining the natural cycle of the uterus.

When I began studies of menstruation in the Rhesus monkey, in 1920, it was soon apparent that very often the events of the cycle are similar to those of the human cycle as generally understood; that is, ovulation occurs about the middle of the interval between two menstrual periods; the corpus luteum is therefore present during the premenstrual phase (for which we now know it is responsible), and its retrogression is contemporaneous with the menstrual breakdown. On the other hand it turned out[4, 5] that in Rhesus there are often menstrual cycles without ovulation, therefore without the corpus luteum and consequently without premenstrual changes in the endometrium. In such cycles the bleeding occurs from an endometrium in the interval stage (compare Figs. 1 and 2).

Such a conclusion, already foreshadowed by the observations of Heape and Van Herwerden, has been amply confirmed, as regards the monkey,

*Read, by invitation, at the Sixty-Fourth Annual Meeting of the American Gynecological Society, White Sulphur Springs, W. Va., May 22 to 24, 1939.

by Hartman[12] and several other investigators, and has been reliably reported for several other primates and Homo. (For a summary of the evidence see Hartman[13] and Rock, Bartlett and Matson.[18]) It contradicted, however, the most plausible and best attested theoretical explanation of the menstrual cycle then current, that commonly called the Schroeder-Meyer hypothesis. This conjecture, formed by experienced gynecologists who studied only human tissues, states that menstruation is caused in some way by the corpus luteum hormone, or as it would now be more precisely stated, by the withdrawal of the corpus luteum hormone. It is therefore absolutely dependent on a preceding ovulation,

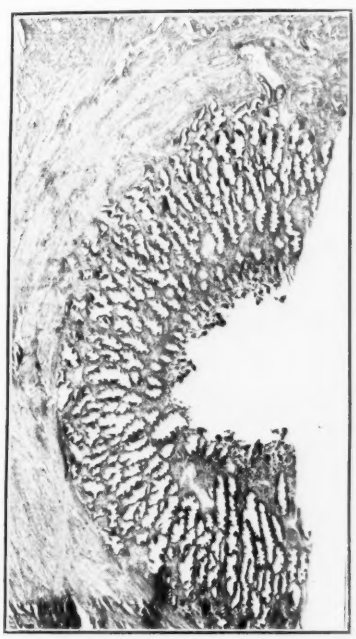

Fig. 1.

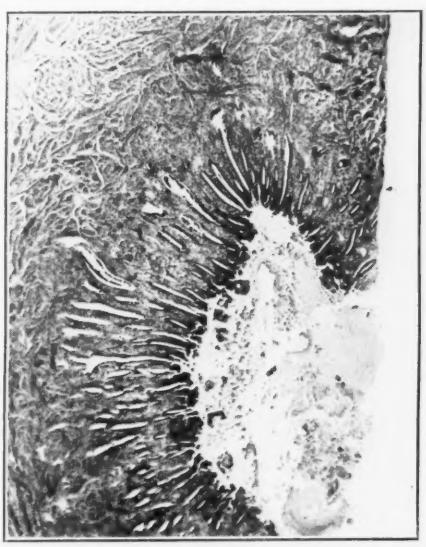

Fig. 2.

Fig. 1.—Ovulatory menstruation, second day (Macaque C.56).
Fig. 2.—Anovulatory menstruation, third day (Macaque B.128, courtesy of Dr. G. W. Bartelmez).

and is inevitably associated with a "premenstrual" state of the endometrium brought about by the corpus luteum—"Ohne Ovulation, keine Menstruation." Bleeding from the uterus, without a corpus luteum, however regularly cyclic it might be, however exactly it resembled ovulatory menstruation in all outward aspects, could not be accepted as menstruation by those who accepted the hypothesis. For them, the concept of menstruation without a "premenstrual" endometrium seemed as difficult as do some of the unfamiliar deductions from the relativity theory to those of us who learned our physics (if at all) only upon the Newtonian basis.

Bartelmez[3] pointed out that in specimens of the human endometrium obtained during menstruation, the only invariable menstrual changes

are vascular in nature. Recently, direct observation of the menstruating endometrium under low powers of the microscope has been achieved by Markee, by the ingenious method of watching small grafts of endometrium growing in the anterior chamber of the eye. Such grafts behave as the same tissue did when at its original site; they bleed during menstruation and after deprivation of estrin. Markee's observations have been reported at scientific meetings and will appear shortly in the Carnegie Contributions to Embryology. He finds that natural menstruation in the grafts proceeds in a regular sequence, with first a phase of constriction of the coiled arteries. As each of these arteries contracts, the region it supplies is rendered ischemic for several hours. After this the artery relaxes, and the blood flow is resumed, but here and there the capillaries of the endometrium, weakened or damaged by the ischemia, rupture and set up temporary small local hemorrhages.

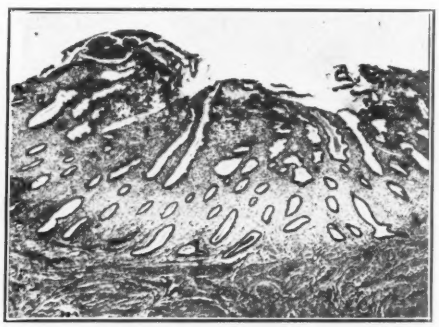

Fig. 3.—Menstruation from an early premenstrual endometrium, first day (Macaque C.19).

The confluence of these local hemorrhages constitutes the total menstrual breakdown. It is a significant fact that the vascular changes observed by Markee are alike whether or not the process is associated with ovulation. The only difference between standard ovulatory menstruation on one hand, and anovulatory menstruation or estrin-deprivation bleeding on the other, is that in the first case, and not in the second, the corpus luteum hormone has been present and has produced the so-called premenstrual changes. In the first case the uterus bleeds from a premenstrual endometrium; in the second case it bleeds from an interval endometrium. These facts are sufficient to show that ovulation is not a necessary antecedent to menstruation.

If this be true we might expect the occasional occurrence of intermediate types of menstruation, when (for example) some accidental upset of the ovulatory cycle sets up a stimulus to menstrual breakdown before the corpus luteum has had time to build up a completely premenstrual endometrium. Such a case, in the monkey, is illustrated in Fig. 3; the menstrual flow occurred five days prematurely, apparently as the result of an exploratory laparotomy with removal of one tube. By comparison with Figs. 1 and 2, it will be seen that the histo-

logical state is intermediate between that of ovulatory (Fig. 1) and anovulatory menstruation (Fig. 2). Bartelmez[3] has described human specimens showing various evidences of menstrual changes of intermediate character.

Before the era of experiment with the ovarian hormones, it was supposed by some that the corpus luteum induces menstruation by some sort of positive effect on the uterus, its presence and activity building up the endometrium to a hemorrhagic phase. Others (e.g., L. Loeb[16]) with closer approach to the truth recognized that the hemorrhagic phase is related to retrogression of the corpus luteum and withdrawal of its function. To me, as I became more and more familiar with anovulatory cyclic bleeding in the monkey, and found that I could in no wise distinguish it from menstruation of the orthodox type, except by exploration of the ovaries and microscopical study of the endometrium, it seemed that any hypothesis upon which progress could be

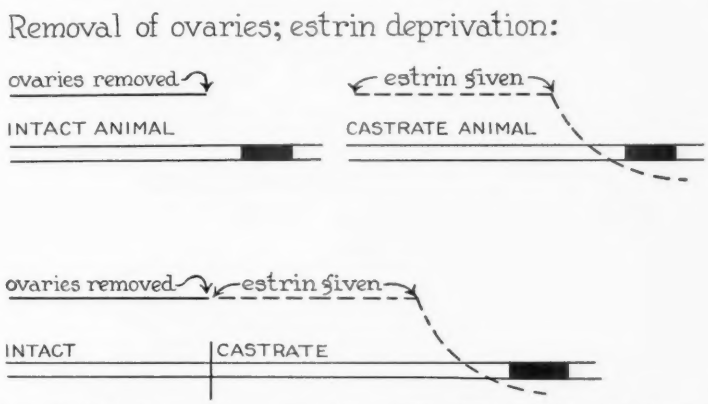

Fig. 4.—Illustrating the experiments of Allen, 1927, 1928. In this and the following graphs the black bars indicate uterine bleeding.

based must at least tentatively accept anovulatory cyclic bleeding as true menstruation. Such a hypothesis could not demand a corpus luteum and the premenstrual state as necessary, and it could only define menstruation as "periodic bleeding from the normal uterus," without further limitation. On such a hypothesis, it seemed to me that menstruation might indeed be due rather to withdrawal of some stimulus or other, than to any positive action of the corpus luteum. Leaving to the future any conjecture as to what it was that might be withdrawn when the corpus luteum retrogresses, and what when anovulatory menstruation takes place, I formulated privately what I called the "hypothesis of x-withdrawal," i.e., that menstruation is due to the withdrawal from the body of a substance the loss of which temporarily disturbs the endometrium.

I did not print the conjecture, for I had no idea what my "x" might be; but a few years later, after the isolation of the estrogenic hormone by E. Allen and Doisy, Allen announced[1, 2] a more specific

hypothesis of the same sort which was supported by experimental evidence. He found that removal of both ovaries from a mature Rhesus female will often cause within a few days a single period of menstruation-like bleeding. He then administered to the castrate monkey a course of the estrogenic hormone and found that discontinuance of the estrin also causes a period of bleeding. In another group of experiments administration of estrin was found to postpone the bleeding caused by oophorectomy.

On this basis Allen formulated the estrin-deprivation hypothesis, which suggests that natural menstruation is due to temporary cyclic reduction of the amount of estrin available in the body. Estrin is the *x*-substance of my private meditations.

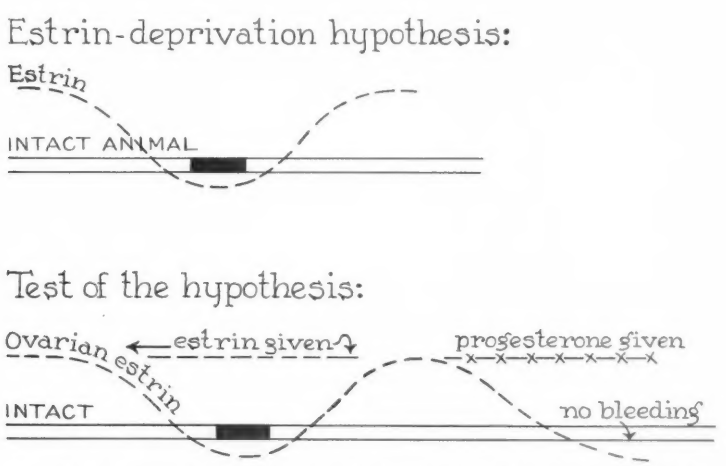

Fig. 5.—In the lower figure the natural level of estrin is shown fluctuating cyclically, not as a fact, but to show how the actual results of injecting the ovarian hormones bear on the estrin-deprivation theory (Corner, 1935; Corner and W. M. Allen, 1936).

Subsequent quantitative experiments, including especially those of Zuckerman[21] have shown that not only total deprivation but also mere lowering of estrin dosage below a certain level will produce the bleeding. The word "deprivation," as used in this connection, is therefore to be taken in a relative sense.

From this hypothetical explanation of menstruation, in its simple original form, it follows that if the estrin level can be maintained by administration of the hormone, natural menstruation should not occur. This I attempted in monkeys,[7] with negative results; that is to say, daily doses of estrone (in the form of progynon) presumably within the physiological range, did not interfere with the first menstrual period due after the beginning of the injections.

On the other hand administration of the corpus luteum hormone, progesterone, in small doses promptly inhibits natural menstruation in experimental monkeys.[7, 10] Smith and Engle[20] and Engle, Smith and Shelesnyak[11] found that bleeding induced in castrate monkeys by

a decidedly vigorous form of estrin deprivation (discontinuance of estrin injections with simultaneous discontinuance of gonadotropic hormone, plus castration) was prevented by crude progestin. Prevention of ordinary estrin-deprivation bleeding by the use of progesterone has been demonstrated by Hisaw[14] and Corner.[9] The discontinuance of a course of progesterone injections of suitable dosage invariably causes the menstruation-like bleeding.[9, 11, 14, 21] In formulating a satisfactory theory of menstruation, we must therefore take into consideration progesterone deprivation as well as estrin deprivation; the corpus luteum shares with the estrogenic endocrine tissue of the ovary the property of causing, by its abrupt removal, breakdown of the endometrium.

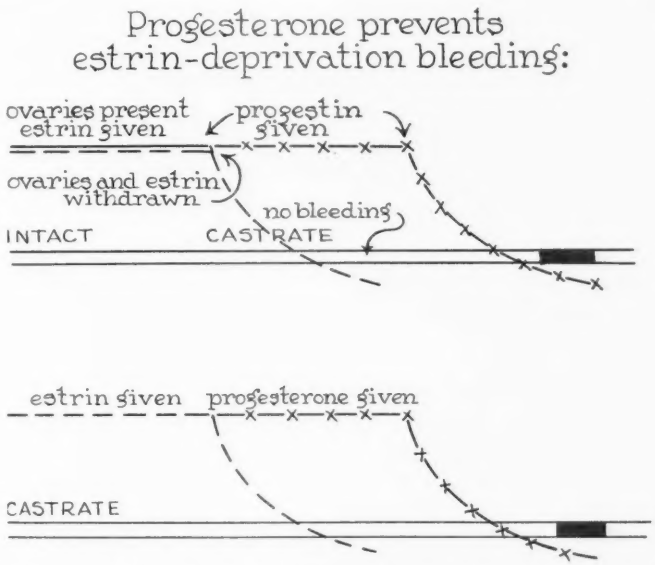

Fig. 6.—The upper figure illustrates the experiments of Smith and Engle, 1932, and Engle, Smith and Shelesnyak, 1935. The lower figure represents the results of Hisaw, 1935, and Corner, 1938. Estrin-deprivation bleeding is postponed by progesterone; discontinuance of progesterone is then followed by bleeding.

Markee states that when bleeding is produced in one of his intraocular endometrial grafts, by withdrawal of either hormone, he witnesses the same sequence of ischemia and hemorrhage that occurs in spontaneous menstruation.

A further step was taken in the experiments of Zuckerman,[21] of Corner[9] and of Hisaw and Greep[15] in which estrone was given in quantity sufficient to build up the endometrium and to cause bleeding if it had been discontinued. While this course of estrone was being given continuously, a ten-day course of progesterone was given and stopped. A few days thereafter menstruation-like bleeding began, in spite of the continued administration of estrone; in fact, bleeding could not now be prevented unless the daily dose of estrone was increased to many hundred international units. I have given elsewhere[9] a de-

tailed experimental analysis of this finding, and have shown that it is best explained by supposing that progesterone has the property of suppressing the effect of estrin upon the endometrium. What chemical and physiological reactions give rise to such interactions of the ovarian hormones is for the future to determine. Pincus and Zahl[17] and Smith and Smith[19] have probably obtained a clue by their studies of the metabolism of the estrogens, which show that progesterone causes an increase of total urinary excretion of estrogen and the conversion of estrone to estriol, and at the same time protects the estrogenic hormones from destruction while in the body.

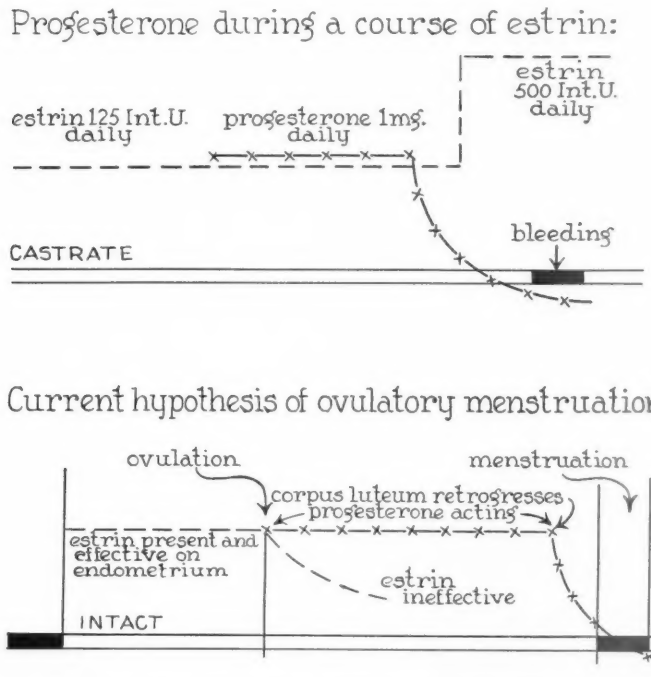

Fig. 7.—The upper figure illustrates the production of bleeding after discontinuance of a course of progesterone, in spite of continued and even more intensive estrin treatment. The dosage shown is that of the author's experiments (Corner, 1937, 1938); similar results were obtained by Zuckerman, 1937, and by Hisaw and Greep, 1938.

These facts enable us to construct a relatively simple hypothesis of the normal cycle which is really a modified form of the estrin-deprivation hypothesis.

We start with the postulate that progestin in some way or other has the property of suppressing the menstruation-preventing power of estrin, while itself holding off menstruation. Then in the normal cycle the uterus will not bleed during the first half ("follicular phase") because the ovaries are furnishing estrin. It will not bleed during the second half of the cycle ("corpus luteum phase") because the corpus luteum is furnishing progesterone. The production of estrin in all

probability continues. By our assumption, however, the corpus luteum is suppressing the protecting effect of estrin; therefore when the corpus luteum undergoes retrogression, the animal is suddenly deprived of the action of both estrin and progesterone, and the endometrium breaks down. Ovulatory menstruation is thus a special case of estrin-deprivation bleeding.

This explanation of the normal cycle is not contradicted by any known facts. It will be observed that it does not necessarily call for a rise and fall of estrin production by the ovaries, for the cyclical presence and absence of the corpus luteum is sufficient to cause a periodic phase of ineffectuality of estrin upon the endometrium.

This scheme does not of course explain anovulatory menstruation. In anovulatory cycles there is no coming and going of the corpus luteum to cause hormone deprivation. Indeed in the monkey I have not been able to see any change in the ovary that can be correlated with the onset of anovulatory menstruation as we can correlate retrogression of the corpus luteum with ovulatory menstruation. One might expect to find beginning atresia of a large follicle, or some comparable histologic cause of estrin deprivation, but I have compared in detail, in serial sections, the ovaries of two monkeys killed during actual anovulatory menstruation with two killed during the interval of the anovulatory cycle, and have not detected any significant difference. It is, however, conceivable that fluctuations of estrin level can occur without morphologic variation in the ovary, and perhaps it will turn out in the end that the give and take of the pituitary-ovarian (or of the pituitary-ovarian-adrenal) relationship does produce in cyclic fashion an actual estrin deprivation. In this case anovulatory menstruation should be preventable by administration of estrin. To test the matter by experiment in monkeys will be tedious indeed, for the time of year when anovulatory cycles prevail is also a time of menstrual irregularity. It will be necessary to prove the absence of a corpus luteum by surgical exploration, then to administer the estrin; but if menstruation fails to occur its absence might be due to the experiment or it might be merely summer amenorrhea. A long series will be required to be significant. Meanwhile we might well keep in mind other possibilities, for example the production in the ovaries of small quantities of progesterone-like or androgen-like hormones, which might counteract estrin in the anovulatory cycle as we suppose progesterone to do in the ovulatory cycle.

This last is pure conjecture; what I hope has been clearly brought out is the probability that hormone-deprivation is the cause of cyclic uterine bleeding, and the fact that the presence of a corpus luteum is not essential for menstruation.

We may suppose that there is a fundamental cycle of pituitary-ovarian balance, which in primates causes periodic uterine hemorrhage, whether ovulatory or anovulatory. As Hartman[12] has pointed out, this cycle may or may not reach its fullest development, which is characterized by maturation of an ovarian follicle and the formation

of a corpus luteum. When ovulation does occur, however, it is geared to the fundamental cycle, and we then have premenstrual changes during the latter half of the cycle. In monkeys the menstrual cycles quite often do not reach the stage of completeness at which ovulation occurs, in humans anovulatory cycles are rare and occur most often during the earliest years after puberty and the latest before the menopause.

We are quite ignorant as to the mechanism by which a drop in hormone level causes the resultant vascular changes in the endometrium. Estrin-deprivation bleeding is an acute affair associated with an abrupt fall in level of the hormone, and it soon ceases and does not recur if the estrin level remains low. Everyone who has studied it experimentally has made conjectures involving the notion of vasoconstrictor effects produced by the deprivation, but no one has yet hit upon the intermediate steps between the estrin deprivation and the ischemic phase.

An interesting conjecture, differing somewhat from the hormone-deprivation hypothesis, has been put forward recently by Smith and Smith,[19] who conjecture that the bleeding of menstruation is caused not by deprivation of estrin, but by its conversion into a nonestrogenic by-product which is toxic to the endometrium. No doubt other variations upon this theme will be offered and subjected to experimental test; but all such hypotheses will agree, as I have maintained here, that menstrual bleeding is caused by fluctuations in levels of the ovarian hormones. It follows that noncyclic and therefore pathological bleeding may also be caused by defectiveness, in amount, proportion or kind, of these hormones. This etiologic concept taken alone will perhaps be acceptable to all, but taken in connection with the strict corpus luteum theory of menstruation, it leads to a conclusion unacceptable under that hypothesis; for it tells us that after all there are not two different and distinguishable kinds of bleeding from the uterus, namely the normal and cyclic kind called menstruation, and the irregular or continuous kind called pathologic under various names such as menorrhagia and metrorrhagia. When the existence of anovulatory menstruation was first proved in the monkey, and suspected in the human, it was easy, but it was wrong, for objectors to call that kind of menstruation "pathologic bleeding" as if a sharp line could be drawn. The modern hypothesis hints to us that much of the functional pathologic bleeding is due to hormone deprivation or imbalance, and therefore we must expect a series of types of hemorrhage from normal menstruation through every grade of disturbance to the most severe metrorrhagia. That clinical studies based on this idea are already hopefully under way is shown by such work as that of Smith and Smith,[19] presented at the 1938 meeting of the American Gynecological Society. Such progress is ample recompense for the abandonment of an untenable theory, for it bids us hope that those same hormones that control the normal cycle will help us to control its aberrations and at last to banish the spectre of uterine hemorrhagic disease.

SUMMARY

In castrate monkeys menstruation-like bleeding is caused by sudden discontinuance of a course either of estrogenic hormone or of progesterone. When the estrogen and progesterone are given simultaneously in suitable amounts, bleeding occurs if the progesterone is discontinued even though sufficient estrogen to prevent bleeding is still being administered. This observation offers a possible explanation of natural menstruation on the basis of recurrent action and inaction of the corpus luteum. Anovulatory menstruation offers a more obscure problem. The mechanism by which deprivation of the hormones sets up a disturbance of the endometrial blood vessels is still unexplained.

From these considerations it is probable that pathologic uterine bleeding may be caused by fluctuations in levels of the ovarian hormones, and that no sharp distinction exists between menstruation and functional metrorrhagia. Such a concept opens the possibility of ultimate control of uterine hemorrhagic diseases.

The author's experiments have been supported by grants from the Rockefeller Foundation and the Markle Foundation.

REFERENCES

(1) *Allen, E.:* Contrib. Embryol. **29** (Pub. Carnegie Inst. Washington, No. 380): 1, 1927. (2) *Idem:* Am. J. Physiol. **85:** 471, 1928. (3) *Bartelmez, G. W.:* Contrib. Embryol. **24** (Pub. Carnegie Inst. Washington, No. 443): 141, 1933. (4) *Corner, George W.:* Contrib. Embryol. **75** (Pub. Carnegie Inst. Washington, No. 332): 75, 1923. (5) *Idem:* J. A. M. A. **89:** 1838, 1927. (6) *Idem:* Harvey Lectures **28:** 67, 1934 (also in Medicine **12:** 61, 1933). (7) *Idem:* Am. J. Physiol. **113:** 238, 1935. (8) *Idem:* Science **85:** 437, 1937. (9) *Idem:* Am. J. Physiol. **124:** 1, 1938. (10) *Corner, George W., and Allen, Willard M.:* Proc. Soc. Exper. Biol. & Med. **34:** 723, 1936. (11) *Engle, E. T., Smith, P. E., and Shelesnyak, M. C.:* Am. J. Obst. & Gynec. **29:** 787, 1935. (12) *Hartman, C. G.:* Contrib. Embryol. **23** (Pub. Carnegie Inst. Washington, No. 433): 1, 1932. (13) *Idem:* Conf. College de France, VI Colloque Internat., Les Hormones Sexuelles, Brouha, L., ed., **2:** 103, 1938. (14) *Hisaw, F. L.:* Am. J. Obst. & Gynec. **29:** 638, 1935. (15) *Hisaw, F. L., and Greep, R. O.:* Endocrinology **23:** 1, 1938. (16) *Loeb, L.:* Surg. Gynec. Obst. **25:** 300, 1917. (17) *Pincus, G., and Zahl, P. A.:* J. Gen. Physiol. **20:** 879, 1937. (18) *Rock, J., Bartlett, M. K., and Matson, D. D.:* Am. J. Obst. & Gynec. **37:** 3, 1939. (19) *Smith, G. Van S., and Smith, O. W.:* Am. J. Obst. & Gynec. **36:** 769, 1938. (20) *Smith, P. E., and Engle, E. T.:* Proc. Soc. Exper. Biol. & Med. **29:** 1225, 1932. (21) *Zuckerman, S.:* Proc. Roy. Soc. London, B **124:** 150, 1937.

BRENNER TUMORS OF THE OVARY*

With Report of 14 New Cases

Emil Novak, M.D., and H. W. Jones, Baltimore, Md.
(From the Department of Gynecology, Johns Hopkins Medical School)

THE difficulties in the classification of ovarian tumors, especially of the malignant group, are notorious. They are due chiefly to our ignorance of the histogenesis of many types. As a matter of fact, most of the classifications which have been suggested have been based upon general pathologic criteria, plus the enumeration of certain special varieties in which something definite is known as to origin and special characteristics. The Krukenberg tumor is a good example of this group. In recent years it has been possible, chiefly through the work of Robert Meyer, to sift out an important group of tumors which have the common characteristic that they arise from rests developing in the early stages of ovarian development. Another characteristic is the fact that, taken as a group, they are far less malignant than other varieties of ovarian cancer. There is an obvious practical importance in separating out such a group, from the standpoint of prognosis and mortality statistics.

One member of this group of so-called special ovarian tumors, the granulosa cell carcinoma, is relatively frequent, constituting something like 10 per cent of all primary ovarian cancers, so that any comparatively small series of cases of ovarian cancer in which a considerable proportion of granulosa cell tumors happens to be included might well give a less pessimistic impression of the degree of malignancy of ovarian carcinoma than most of us have. The other members of the group, dysgerminoma and arrhenoblastoma, are much less frequent, but they likewise are characterized by relatively low degrees of malignancy.

In former years this special group was made to include a fourth tumor type, the so-called Brenner tumor, but the rather different mode of histogenesis of this neoplasm and the fact that it is essentially benign would seem to necessitate its separation from the other members of this group. The fact that most general pathologists and many gynecologic pathologists are not familiar with this tumor variety, and that it is frequently confused with granulosa cell carcinoma, makes it worth while to discuss its characteristics on the basis of the comparatively large group of cases which we have encountered in our laboratory.

This paper is based upon the study of 17 cases, though only 14 are reported herein, since 3 cases have been previously published (Wolfe and Kaminester,[1] Bland and Goldstein,[2] Te Linde[3]). Most of the cases in our series have been encountered in recent years, though it is certain that many instances must have been overlooked in the earlier years of

*Read at the Sixty-fourth Annual Meeting of the American Gynecological Society, White Sulphur Springs, W. Va., May 22 to 24, 1939.

our laboratory, when this now clearly delineated neoplastic type was rather generally unrecognized.

The first description of what was undoubtedly a Brenner tumor appears to have been by Orthmann[4] in 1899, at least eight years before the publication of Brenner.[5] He applied to the tumor in his case the designation of "fibroma papillare superficiale carcinomatosum ovarii," and it is of interest that in this first description the suggestion is made that the origin may be in the cell aggregations which we now speak of as Walthard islets, thus anticipating the prevalent modern viewpoint as to the histogenesis of these tumors. The designation of the tumor as "papillary" is difficult to understand except that the author evidently related his tumor, which happened to be superficially placed, to the not infrequent superficial fibroadenomas, which frequently are papillary.

The three cases reported by Brenner in 1907 were designated by him as "oophoroma folliculare" and were confused by him with the granulosa cell tumors included in the same report. This confusion is still quite commonly encountered in laboratories of pathology. Brenner's employment of the term oophoroma was based on the idea that the swollen cells found so often in the interior of the epithelial nests which characterize the Brenner tumor are of the nature of ova, a morphologic misinterpretation similar to that which has been made in the case of certain other ovarian tumors, such as the so-called "medullary carcinoma with ovum-like cells."

It was Robert Meyer[6] who in 1932 described the characteristics of the Brenner tumor, distinguishing it sharply from granulosa cell carcinoma, and offering the explanation of histogenesis which is still the generally accepted one. In his analytical review of the literature, he was able to eliminate from this category certain cases which had been reported as Brenner tumors, and to add others which had been incorrectly reported under other designations. With his own 4 cases, he was able thus to collect a total of 22 cases. The first American case, so far as I can ascertain, was that of Geist,[7] reported in 1922, although it was not definitely classified by the author.

Incidence.—It is of interest to note that the three cases reported by Brenner in his original paper of 1907 were all observed by him within a period of one and one-half years, which would give a false impression of the frequency of this neoplasm. Meyer encountered only 4 cases in the large material of his laboratory during twenty years, and von Szathmáry[8] more recently reported an incidence of 5 cases among 1,114 ovarian tumors in the Budapest Clinic during fifteen years. In our own laboratory we have observed 17 instances, in a material of more than 48,000 case specimens, though a further review of all this material would undoubtedly reveal many more. On the other hand, it must be added that several of our cases were slides or specimens sent in to us from other clinics for diagnosis. The tumor must, therefore, be looked upon as a very rare one, though with other commonly unrecognized types, not nearly so rare as the literature would indicate. Meyer, in 1932, was able to collect only 22 cases, but in 1933 Szathmáry collected 40, including 5 of his own, and in the most recent review of the subject, that of Varangot[9] (1938), 108 cases were collected, including the 3 reported by the author himself. Our 14 new cases would raise this to 122.

Histogenesis.—The most interesting aspect of the Brenner tumor is the question of its histogenesis. As already mentioned, Brenner himself believed the source to be the follicle, because of the ovum-like structures seen so often within the cell

nests, and because of the superficial resemblance of the latter themselves to follicles. The condensed ovarian tissue about the cell islands was even interpreted as representing the theca folliculi. Meyer's explanation of the histogenesis of these tumors, while difficult of proof, has been accepted by practically all subsequent writers as probably correct. According to this view, the tumor arises from the islands of indifferent cells first fully described by Walthard[10] in 1903, though Plaut[11] credits Werth with an earlier description as far back as 1887. Akagi,[12] a pupil of Walthard, restudied the problem in 1928, his findings being essentially like those of Walthard himself.

The Walthard inclusions may be found in the superficial portion of the ovaries, and even more frequently, the tubes and uterine ligaments, especially in the newborn and young child, but occasionally in the adult. They may consist of nests of cells resembling squamous epithelium, often showing cystic hollowing, and perhaps actually converted into tiny cysts (Fig. 1). On the other hand, the inclusions

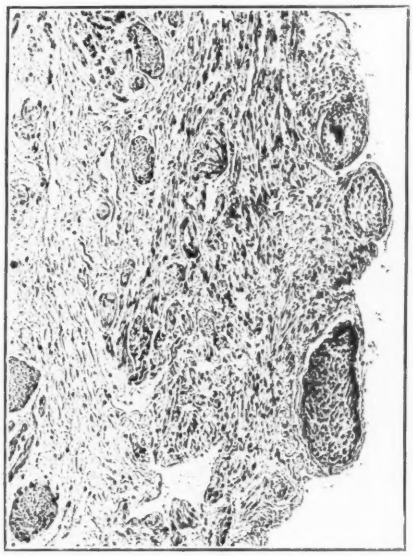

Fig. 1.

Fig. 2.

Fig. 1.—Walthard islets, resembling plaques of squamous epithelium, on surface of ovary near hilum. In the medulla of this same ovary (Case 5) a small Brenner tumor was found.

Fig. 2.—Walthard island at another portion of same ovary shown in Fig. 1. This likewise was near hilum, and it appears as an acinus-like space lined by columnar epithelium.

may take the form of glandlike spaces lined by columnar, perhaps ciliated, epithelium, with at times definite mucoid activity (Fig. 2). In other words, the transmutations of the epithelium are much like those exhibited by the epithelial nests of the Brenner tumors, constituting at least circumstantial evidence of an origin of the latter from the Walthard rests. In addition to the embryologic rests described by Walthard, one must consider the possibility that Brenner tumors may arise from the areas of epithelial metaplasia found not infrequently on the surface of the ovaries which are the seat of chronic peri-oophoritis. One often sees striking metaplasia of the peritoneum and germinal epithelium under such circumstances, with at times the formation of areas of stratified epithelium, not infrequently cystic, and quite like the Walthard islands of indifferent cells (Fig. 3). Whether such islands can be the starting-point of Brenner tumors is a question, though a number of authors have suggested this possibility.

Another possible source has been suggested by Schiller,[13] chiefly on the basis of the microscopic study of one of the cases reported by him in 1934. In this

case he found what he interprets as an abnormal persistence of the embryonic relationship between the rete ovarii and the epoophoron tubules in the hilum of the ovary. If one accepts the view held by some that these two structures have a totally different origin, the epoophoron tubules from the Wolffian body and the rete from the germinal nucleus, it would be difficult to explain any very intimate relationship. On the other hand, the present-day tendency is to accept the view championed by Fischel,[14] and others that most of the ovarian components, including the medullary tubules, the granulosa and even the epoophoron tubules, are derivatives in situ of the mesenchyme. Schiller therefore postulates that if Wolffian epoophoron tubules, developing in the neighboring Wolffian body mesenchyme, are included in the ovarian hilum, they possess the potentiality to form epithelium like that which normally characterizes the urinary tract. In other words, Schiller, rather laboriously, as it seems to us, compares the epithelial variations in Brenner tumors, including even the pseudomucinous changes so often seen, with those to be found in the urinary tract.

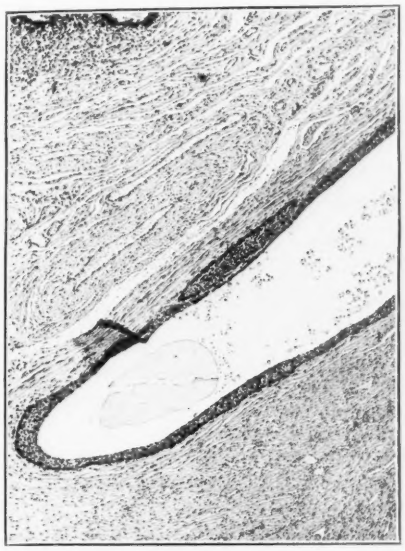

Fig. 3.

Fig. 4.

Fig. 3.—Squamous metaplasia of peritoneal cleft in adhesions between tube (left) and ovary (right).

Fig. 4.—Small medullary Brenner tumor in Case 3.

Schiller is careful to say that his explanation of the origin of some Brenner tumors does not conflict with the more generally accepted viewpoint of Meyer, above discussed, suggesting that different Brenner tumors may have different origins. He offers as further evidence of his hypothesis the fact that the local topography of some Brenner tumors indicates an origin from the hilum. This may be freely admitted, for certainly at least some of these neoplasms, as shown for example in our Cases 3, 4, and 5, do arise in the hilum (Fig. 4). On the other hand, frequently they are cortical, as in our Cases 7, 8, and 13. The seat of origin of such tumors can naturally be best studied in very small growths, for in the large tumors, or those associated with large cysts, the normal ovarian geography is usually blotted out. It would be difficult, as well as unnecessary, to invoke Schiller's theory in the explanation of such a tumor as that shown in Fig. 5, which is located just beneath the surface of the ovary. Moreover, Walthard islands may be found in the region of the mesovarium as well as in other parts of the ovary, so that it seems to us that Meyer's theory is still the one supported by the best evidence. One can, as a

matter of fact, trace all transitions from mere Walthard rests which are not Brenner tumors, to those in which there is only slight surrounding fibromatous reaction and nodule formation, to the larger tumors in which both epithelial and fibromatous elements are present in large amount.

Clinical Characteristics.—Brenner tumors of the ovary occur most frequently in women beyond the menopause, the usual statement being approximately correct, that more than 50 per cent occur beyond the age of 50. The ages of the patients in our own series were as follows: 71, 25, 37, 43, 36, 49, 28, 37, 45, 45, 62, 63, 27, 35. The oldest patient was therefore 71, and the youngest 25. So far as I know, no genuine Brenner tumor has been reported in a child. In our own series, therefore, the age range is definitely lower than that commonly reported, only 3 of our 14 patients being more than 50 years of age. This is probably to be explained by the fact that a considerable proportion of our tumors were very small, being discovered incidentally, either at operation or in the laboratory in patients operated upon for other lesions. In contrast with other tumors of the ovary, certainly those

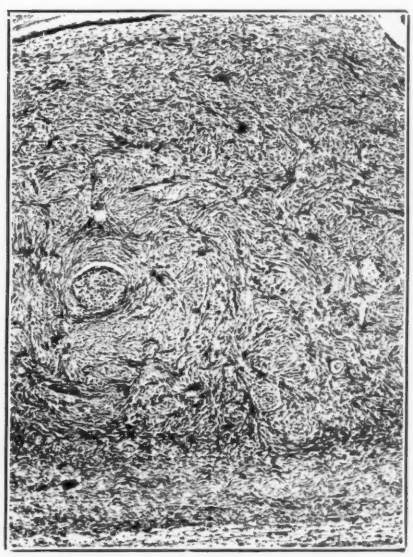

Fig. 5.

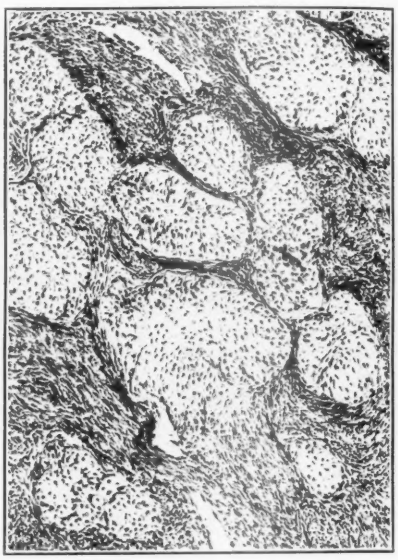

Fig. 6.

Fig. 5.—Definitely cortical Brenner tumor, only a few millimeters in diameter, just beneath germinal epithelium of cortex (Case 7).

Fig. 6.—Typical histologic picture of solid Brenner tumor (Case 6).

of malignant type, the growth of Brenner tumors is likely to be slow. Furthermore, they produce no very characteristic symptoms, so that the high incidence in elderly women loses some of its significance, as the tumors which come to removal might well have been present for a good many years. Ascites seems to be rare, though it was noted in one of our cases (Case 9). Eleven of our 14 patients were white, 3 colored. Three (Cases 2, 13, and 14) were pregnant at the time of operation. The menstrual history is not at all characteristic, and in our premenopausal cases the occasional abnormality was obviously due to associated lesions and not to the tumors. Endometriosis was an associated finding in 1 patient (Case 5).

Pathology.—The size of the tumors varies between very wide limits. Some are of microscopic size, while others may assume enormous proportions, even when not associated with cystadenoma. The largest solid Brenner tumor recorded appears to be that of Neimann,[15] which weighed 15 pounds, and which, to judge from the description and illustration, is a genuine tumor of this variety. The gross appearance of the solid tumors is quite similar to that of fibroma, although there is frequently

a yellowish tint to the cut surface. There is very little tendency to necrosis or cystic degeneration in the solid variety, and hemorrhage is uncommon. No definite capsule exists, although the surrounding ovarian stroma is more or less compressed.

From a microscopic standpoint there are two essential constituents, viz., the characteristic nests of epithelial cells and the fibromatous connective tissue groundwork surrounding the epithelial islands (Fig. 6). Both of these must be present to justify the diagnosis of Brenner tumor, a fact overlooked by some authors who apply the term to the epithelial rests themselves. This mistake, for example, was made by Plaut, whose Cases 6, 7, and 8 do not seem, for the above reason, to be properly classed as Brenner tumors. Why the fibromatous reaction occurs with some rests and not others can be explained only on the general basis of the cytogenous influence (Fischel) exerted by the epithelium not only in Brenner tumors but also in other conditions, such as endometriosis. With the latter, the endometrial epithelium excites an endometrial stromalike reaction about the glands, though in some cases this may be absent.

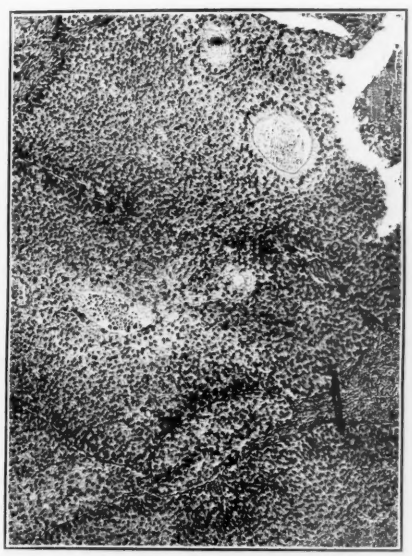

Fig. 7.

Fig. 8.

Fig. 7.—Unusually bulky epithelial fields in Brenner tumor (Case 1). Note the columnar epithelium, with peripheral nuclei, in the small cystic cavity toward top (see text).

Fig. 8.—Cystic hollowing of epithelial islands in medullary Brenner tumor of Case 5.

The epithelial nests may be round or cylindrical, very small or extremely bulky, as in some of our cases (Fig. 7). The striking characteristic is the uniformity of the cells. In many islands even the cells close to the connective tissue margin lack the compactness and the intensity of nuclear staining seen in ordinary epithelial neoplasms, malignant or benign. In others they do seem slightly more closely packed. The cells are rather large and polyhedral, with small nuclei of ovoid shape and striking uniformity, and with no suggestion of overactivity, so that they do not in any way suggest malignancy. The term carcinoid as applied to these tumors by Frankl[16] is not a good one, except perhaps as referring to the distribution of the nests in the connective tissue stroma.

In most tumors there is some tendency, often very widespread, to central cystic degeneration of the epithelial nests (Fig. 8). In the early stages of this there results a small central cavity filled with a rounded protoplasmic mass which superficially resembles an ovum, and which was so interpreted by the earlier writers (Fig. 9). For example, it was because of this resemblance to a follicle with central

ovum that these tumors were originally designated by Brenner himself as oophoroma folliculare. The slightly condensed surrounding ovarian tissue layer was even thought to represent the theca folliculi.

When, as is frequently the case, the central liquefaction is more advanced, the entire nest may be converted into a tiny cyst with little or none of the original epithelium left, though most often a number of layers persist. Meyer and others have called attention to the difference between the innermost layer of the epithelium in these partially cystic nests, and the corresponding layer in the folliculomatous variety of granulosa cell tumors. In the former the nuclei are placed peripherally, i.e., away from the lumen (Fig. 7) while in granulosa cell tumors they are at the central pole of the cells. On the other hand, in many of the cell aggregations which show central liquefaction, the cavity is lined irregularly by degenerating cells rather than by any well-ordered layer.

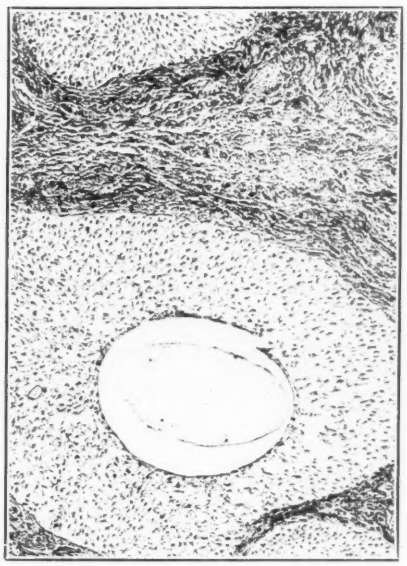

Fig. 9.

Fig. 10.

Fig. 9.—Ovumlike appearance of degenerated protoplasmic center of partially cystic epithelial nests (Case 6).

Fig. 10.—Pseudomucinous columnar epithelium lining cystic center of cell nest (Case 11).

The most interesting feature of the epithelium, however, is the fact that its superficial layer, in the small cystic cavities, so common in the cell nests, may assume a mucoid columnar form quite like that which characterizes the ordinary pseudomucinous variety of cystadenoma (Fig. 10). There is thus produced a superficial resemblance to a many-layered gland (''intra-epithelial gland''). This was described by Geist as far back as 1922, although this observation appears to have been overlooked by subsequent writers. Meyer and von Szathmáry find that this inner layer of cells contains glycogen, which, incidentally, is not found in granulosa cell tumors. The latter, on the other hand, show lipoid material, which is lacking in the Brenner tumors. The fluid content of the cystic cavities of the latter is of either mucoid or colloid nature, or may be a combination of these.

One can see in one and the same section solid epithelial nests, those with a superficial layer of pseudomucinous epithelium lining the small central cavities, and areas in which the pseudomucinous epithelium alone is to be seen lining gland like spaces and perhaps large cystic cavities (Fig. 11). The latter, in other words,

present the characteristic picture of pseudomucinous cystadenoma, and, as a matter of fact, large cystadenomas may thus arise, with perhaps no trace of their original source other than a small nodular thickening in which the typical Brenner pattern may still be preserved. There is no doubt, therefore, of the correctness of Meyer's observation that at least a certain though small proportion of pseudomucinous cystadenomas have their origin in Brenner tumors, though the majority no doubt are to be interpreted as teratomas in which certain entodermic elements have blotted out other constituent tissues, just as in struma ovarii it is the thyroid tissue which has overridden and blotted out other teratomatous elements.

There is logic, therefore, in the subdivision of Brenner tumors into the solid and cystic varieties, though it should be remembered that the subdivision is not a sharp one. In other words, even in the solid tumors some degree of pseudomucinous epithelial change may be seen, while in even the large cysts, solid Brenner rests may be found in nodular masses persisting in the cyst wall. Meyer states that serous cystadenomas of the ovary may likewise at times have a similar origin from Brenner tumors, though we have observed no cases of this type.

Fig. 11.

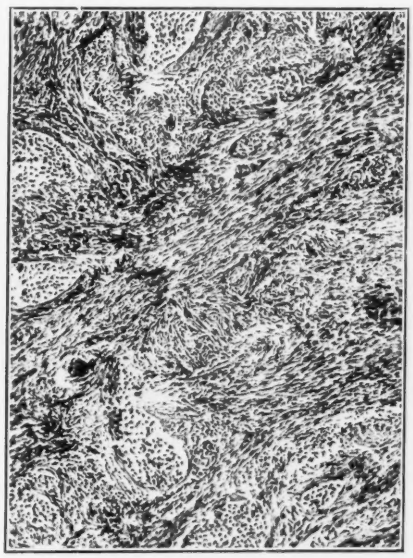

Fig. 12.

Fig. 11.—Pseudomucinous transformation of Brenner rests passing on by easy transition into a large pseudomucinous cystadenoma, part of whose wall is seen below and to left (Case 1).

Fig. 12.—Typical epithelial islands in large ovarian fibroma of Brenner origin (Case 10).

Not only cystadenoma of the ovary, but likewise fibroma may have its origin in Brenner tumors. From time to time in past years solid fibromas have been reported to show epithelial aggregations which have been variously interpreted. Frankl in 1927 reported a group of such cases to which he applied the designation of fibroadenoma ovarii adenocysticum, but, as Meyer has shown, these are properly to be construed as Brenner tumors in which the characteristic connective tissue response has assumed huge proportions, so that tumors weighing many pounds may be produced. The 15-pound tumor reported by Neimann belongs to this group, as does our Case 10, in which the tumor was likewise of large size (Fig. 12). In this case only a moderate distribution of epithelial nests was to be noted in the fibromatous matrix, but in that of Neimann the proportion of epithelium to connective tissue was much greater, if one may judge from the illustrations. The gross picture of Brenner tumors is quite similar to that of fibromas, and there is litttle doubt that

a careful study of many supposedly simple fibromas of the ovary would show them to be of the Brenner variety.

As I have already mentioned, the Brenner neoplasm is to be looked upon as benign. There was a tendency not so many years ago to class them with the malignant tumors of the ovary, perhaps because of their earlier confusion with granulosa cell tumors. Not a single case in the literature, however, has recurred after removal, though Mandelstamm[17] cites an instance reported by Tavildaroff, in a rather inaccessible Russian source, of a Brenner tumor which is said to have recurred in the other ovary. This case seems very doubtful, and, if it really was a Brenner growth, was more likely to have been an instance of bilateral tumor. Similar bilateral tumors have been reported by Schiffman[18] and others.

Absence of Endocrine Influence.—A point which has received some discussion is as to the influence, if any, of these tumors upon the endometrium. The capacity of the granulosa cell tumor to produce hyperplasia of the endometrium and menstruation-like bleeding in postmenopausal women is well-known, and is readily explainable by their histogenesis and their capacity to produce the estrogenic hormone. Only Schiffman seems to have noted hyperplasia of the endometrium and uterine bleeding in association with Brenner tumors, and his illustrations would seem to bear this out. However, this isolated observation loses its significance now that we know that hyperplasia of the endometrium may at times be found in post-menopausal women in the entire absence of any tumor, and that it may be clinically associated with uterine bleeding. For this reason we have likewise had to modify our former view that the finding of well-marked hyperplasia of the endometrium long after the menopause is presumptive evidence of granulosa cell carcinoma, even though no tumor is palpable. Since there has been no confirmation of Schiffman's observation by other authors, it seems highly probable that the endometrial hyperplasia found in his case was coincidental, and that it was not causally related to the Brenner tumor in the ovaries.

In only one of our own cases (Case 12) was postmenopausal bleeding seen in association with a Brenner tumor, though unfortunately in this case the endometrium was not available for study. Moreover, in this case there was present a large pseudomucinous cystadenoma. As in Schiffman's case, and for the same reason, it seems likely that the bleeding in our patient was probably not related to the presence of the Brenner tumor. Postmenopausal bleeding is said to have occurred likewise in a number of other cases in which the endometrium was not studied (Schiller, Abraham,[19] Kleine,[20] Freund,[21] Fauvet[22]) but in spite of this there is no reason to think that this was due to any such direct endocrine effect upon the uterus as is produced by the granulosa cell tumors. As a matter of fact, the uterus in old women with Brenner tumors has often been described as typically senile and atrophic. When the tumor occurs during the menstrual life, no characteristic effect upon menstruation is noted, as I have previously mentioned.

CASE REPORTS

CASE 1.—(Gyn. Path. 47851.) For the privilege of including this case in our series we are indebted to Dr. S. A. Chalfant, of Pittsburgh. The patient was 71 years old. A normal menopause occurred at 54, and there had been no bleeding since. There had been no pregnancies. A large tumor in the lower abdomen had been noticed by the patient several months before admission.

Operation revealed the tumor to be a large cystic growth of the right ovary, measuring 19 cm. in diameter. About half of this tumor was represented by a thin-walled cyst with smooth lining, while the remainder was solid, presenting a dense structure resembling fibrous tissue, arranged in interlacing bundles, and containing small spicules of calcified material. The solid fibrous portion was grayish in color, with blotchy areas of light yellow, and there were a number of tiny cystic areas.

Microscopically this case presents a beautiful illustration of transitional changes between a solid Brenner tumor and a pseudomucinous cystadenoma. The solid parts of the tumor show the characteristic epithelial nests embedded in large areas of fibromatous stroma. In places, however, the nests show hollowing, with an inner

lining of tall mucoid epithelium, which in adjoining areas completely replaces the stratified epithelium, becoming more and more adenomatous, presenting the characteristic picture of pseudomucinous cystadenoma, as seen in the large cyst making up about half the entire tumor.

CASE 2.—(Gyn. Path. 47264.) For the slide of this tumor, and for permission to include the case in our series, we are indebted to Dr. D. R. Meranze of Mt. Sinai Hospital, Philadelphia. The patient was 25 years old, and she was pregnant four months at the time of operation, her complaint being of abdominal pain for two weeks preceding the latter. The previous menstrual history had been entirely normal. Before operation a large tumor was palpable in the right lower abdomen, and this proved to be a solid ovarian tumor about the size of a grapefruit. Microscopically it is a typical fibroma of the ovary, throughout which are discretely scattered large numbers of the characteristic epithelial nests which indicate the Brenner nature of the neoplasm.

CASE 3.—(Gyn. Path. 47031.) This patient was 37 years old, and was operated upon in the Gynecological Clinic of the Johns Hopkins Hospital for the removal of a large myomatous tumor, associated with extensive bilateral adnexitis. Supravaginal hysterectomy with bilateral salpingo-oophorectomy was performed. The routine laboratory examination revealed, only on microscopic examination, a tiny but perfectly typical Brenner nodule situated in the region of the right ovarian hilum. The characteristic cell nests, the fibromatous stroma and the definite pseudoencapsulation of the nodule would seem to leave no doubt as to the nature of this microscopic neoplasm (Fig. 4). No epoophoron or rete tubules could be demonstrated in relation with the tumor.

CASE 4.—(Gyn. Path. 45109.) This patient, aged 43 years, was operated upon by one of us (E. N.) at Bon Secours Hospital for chronic pelvic inflammatory disease. She had had no menstrual period for one year. Aside from the bilateral salpingitis, the left ovary was found to be moderately enlarged, measuring 4.5 by 3.5 by 2.5 cm., and the cut section showed a small, solid, circumscribed fibrous mass surrounded by a capsule of normal-looking ovarian tissue. The tumor seemed undoubtedly to arise in the medullary portion of the ovary. Its structure was that of a typical Brenner tumor of the solid type. No pseudomucinous alteration of the epithelium was to be seen.

CASE 5.—(Gyn. Path. 44210.) This patient, aged 36 years, was operated upon Dec. 3, 1936, because of large uterine myomas, associated with pelvic endometriosis and bilateral endometrial cysts. Menstruation was normal in every way, the patient entering the clinic because of lower abdominal discomfort and because she had noticed a mass in the lower abdomen. A supravaginal hysterectomy with bilateral salpingo-oophorectomy was done.

In addition to the myomas and the endometrial cysts, which need not be described in detail, the routine microscopic examination revealed a tiny microscopic Brenner tumor, measuring 1 by 0.5 mm. in the medulla of one ovary. Fig. 8 will show how typical it is, with the characteristic cell nests embedded in a circumscribed nodule of fibrous tissue arranged in an interlacing whorllike fashion. It is of great interest that in the same section one finds a number of typical Walthard cell nests on the surface of the mesovarium, some of them being of the more common squamous appearance, with cystic hollowing of the interior (Fig. 8), but others appearing as gland lumina lined by tall and partly ciliated epithelium (Fig. 2). This is the only case in which we have found Walthard islets in association with an actual Brenner tumor, and the fact that both are found in the vicinity of the hilum would seem suggestive. Moreover the presence of extensive ovarian endometriosis in this case would seem to indicate a strongly metaplastic tendency, at least to those of us who believe in the doctrine of coelomic metaplasia as the probable explanation of endometriosis.

CASE 6.—(Gyn. Path. 42178.) This patient was 49 years old, a para ii, whose menstruation had been entirely normal in character and amount, and who was operated upon because of large uterine myoma, the operation consisting of supravaginal

hysterectomy and bilateral salpingo-oophorectomy. The right ovary was twice the normal size, and consisted chiefly of a circumscribed nodule which on section was uniformly whitish in appearance. The microscopic picture was that of a typical Brenner tumor.

CASE 7.—(Gyn. Path. 43211.) This patient was colored, aged 28 years, and had had no pregnancies. Her complaint was of a hard mass in the lower abdomen, with pain and leucorrhea, but with no menstrual excess. On April 16, 1936, a supravaginal hysterectomy with left salpingo-oophorectomy was performed, the ovary on this side being large, adherent, and cystic, while the right adnexa were normal. In the routine pathologic examination, a tiny but typical Brenner nodule, from the standpoint of both cell islands and fibromatous stroma, was found just beneath the cortex (Fig. 5). On the surface of the ovary, overlying the nodule, there was a layer of adhesions, and the germinal epithelium beneath these had become tall and columnar, so that it resembled endometrial epithelium. This is a not uncommon finding in cases of peri-oophoritis. The very definitely cortical location of the Brenner nodule in this case would seem to rule out entirely any such explanation as that suggested by Schiller in the case of medullary tumors.

CASE 8.—(Gyn. Path. 38151.) This specimen was sent to the laboratory by Dr. Elbert DeCoursey, Ancon, Canal Zone. It was accompanied by the following clinical note from Dr. DeCoursey. "Operation: Salpingo-oophorectomy, right. The specimen comes from the ovary of a 37-year-old black female who has complained of pain in the right pelvic region. She missed the January menstrual period, but menstruated February 18, and passed some blood each day until March 9. No bleeding since that time. A large mass was palpated in the right side of the abdomen. The surgeon at Colon informs me that the patient had a ruptured ectopic pregnancy, and he excised the right tube and ovary. When I saw the tissue, the thickened right tube had been ruptured, leaving an oval bloody cavity about 5 cm. in length. I have searched, but have been unable to find chorionic villi in multiple sections. In the ovary was a round pearly pink mass about 2 cm. in diameter. It was hard, circumscribed, and seems to be well encapsulated." The "round pearly mass" proved to be a Brenner tumor which apparently had its origin in the cortical zone.

CASE 9.—(Gyn. Path. 39196.) For the sections of this case and for permission to include it in our series, we are indebted to Drs. L. C. Scheffey and Crawford of Philadelphia. The patient, aged 45 years, para i, was admitted to Jefferson Medical College Hospital, April 29, 1929, with a complaint of lower abdominal discomfort of four weeks' duration. She had noticed an enlargement of the abdomen. Menstruation had been normal except for a period of several months when the period had become shortened to two or three weeks. There had been a period of amenorrhea for three months preceding the last menstruation, which occurred one month before operation. Examination showed a nodular mass in the lower pelvis, apparently springing from the adnexa, as the uterus was small and freely movable. The patient stated that the lump felt "like a bag of marbles." At operation by Dr. Scheffey, on May 6, 1929, the tumor was found to be a solid neoplasm of the left ovary. A moderate amount of ascitic fluid was present. The right tube and ovary were normal. Supravaginal hysterectomy and bilateral salpingo-oophorectomy were performed. The patient was apparently well eight years later.

Dr. Scheffey was good enough to send us a section of the tumor, which at that time we incorrectly diagnosed as folliculoma. On subsequent review, however, the tumor was found to be a typical Brenner tumor of the solid variety.

CASE 10.—(Gyn. Path. 42248.) This patient was colored, aged 45 years, and was admitted Aug. 8, 1935, because of a large mass extending to the umbilicus, her chief symptom being profuse menorrhagia. At operation a few days later the uterus was found to be about normal in size, though it showed several small intramural myomas. Attached to the fundus by a definite pedicle was a large solid tumor of the right ovary, the tube being normal. The tumor was 13 cm. in its

greatest diameter, and on section seemed to be a fibroma. On microscopic examination, however, it showed numerous scattered epithelial cell nests, many with central degeneration, and some showing the typical ovumlike appearance of the central protoplasmic mass (Fig. 12). As the uterus was not removed, the endometrium was not available for study.

CASE 11.—(Gyn. Path. 12512.) This patient was 62 years old, and entered the hospital because of great abdominal enlargement and also vaginal bleeding. She had menstruated normally until the age of 22, when menstruation ceased completely, presumably a precocious menopause of endocrinopathic causation. At the age of 60 she began to have bleeding irregularly and scantily, this continuing for six months, followed by cessation for six months, and then reappearance of the bleeding, which had persisted up to the time of admission. The abdominal enlargement was found to be due to a large ovarian cyst, and left salpingo-oophorectomy was done. The right adnexa and the uterus were not removed, being normal in appearance.

The left ovarian tumor measured 21 by 19 by 18½ cm. and microscopic examination showed it to be a benign, multilocular, pseudomucinous cystadenoma. In several areas, however, the wall showed firm, fibrous solid areas, and microscopic examination of these showed the typical picture of Brenner tumors. Most interesting, however, was the gradual transition of these areas into the cystadenoma. In places, the Brenner islands were solid, in others cystic, and in the latter the inner layer was seen to have become tall, columnar, and pseudomucinous (Fig. 10). Gradually the pseudomucinous epithelium dominated the entire picture, producing the characteristic pattern of pseudomucinous cystadenoma.

CASE 12.—(Gyn. Path. 9157.) The patient, aged 63 years, entered the hospital complaining of an abdominal mass and of lower abdominal pain. She had had a large ovarian tumor, presumably a cyst, removed at the age of 24, and she had had a normal menopause shortly after the birth of her last child, at the age of 42. There had been no bleeding since then. The tumor in this case proved to be a large pseudomucinous cyst of the remaining ovary, and this was removed, with the tube. In the walls there was found a solid area which, under the microscope, revealed the typical picture of a Brenner tumor. Here, as in Case 11, one found a gradual transition to and then replacement by the characteristic epithelium of the pseudomucinous cystadenoma. An interesting feature in the Brenner areas was that even some rather large cystic cavities showed a lining of stratified epithelium, with transition to pseudomucinous epithelium.

CASE 13.—This specimen was recently sent to one of us (E. N.) by Dr. E. S. Edlow, of Sinai Hospital, Baltimore, to whom we are indebted also for the clinical data on the case. The patient was a nulliparous white woman of 27, who entered the hospital on Dec. 7, 1938, with a history of amenorrhea from October 6 until two weeks before admission, when vaginal spotting appeared, continuing up to the time of admission. The cervix was rather soft, the uterus somewhat enlarged, the left adnexa negative, but in the right adnexal region there was a fusiform swelling about 1½ cm. in diameter. A presumptive diagnosis of right tubal pregnancy was made, but operation revealed the right-sided swelling to be due to an enlargement of the ovary by a small fibromalike tumor located cortically. As it was thought to be benign, only the tumor-bearing segment of the ovary was resected. Curettage was then performed, revealing what was apparently decidual tissue, and this was confirmed by microscopic examination. The histologic examination of the small ovarian tumor showed it to be a typical solid Brenner tumor.

CASE 14.—For the slide and data concerning this case we are indebted to Dr. George L. Streeter and Dr. Elizabeth Ramsay, of the Carnegie Institute of Embryology. The patient was 35 years old, and she had had previous pregnancies, 5 terminating in abortion, and 1 in premature stillbirth at the seventh month. She was thought to be pregnant again at about one and one-half to two months, when slight vaginal bleeding appeared, persisting for two weeks, when it became much freer. Two days later laparotomy was done, possibly under the suspicion of tubal

pregnancy, though this is not certain. The operation consisted of supravaginal hysterectomy and bilateral salpingo-oophorectomy.

Examination of the specimen in the Carnegie Laboratory showed the uterus to be 65 by 58 by 58 mm. in size, with an implanted ovum, apparently beginning to dislodge, 50 by 20 mm. The left ovary contained a dermoid cyst about 11 by 11 cm., while in the right ovary there was a firm rounded nodule about 15 mm. in diameter near one pole, extending from the medulla to the surface, so that it was difficult to say whether it originated in the cortex or the medulla. Its microscopic examination showed it to be a typical Brenner tumor of the solid variety.

SUMMARY

This paper is based upon the study of 17 cases of Brenner tumor of the ovary, including the 14 new cases herein reported. This brings the total of reported cases to 122, though new instances are being reported more and more frequently. The tumors are benign, and produce no characteristic symptoms. When small they are, therefore, likely to be found only accidentally in operations for other indications. They may, however, reach very large size, in which case they produce discomfort or pain, with perhaps the presence of a mass noticeable to the patient herself. The pathologic characteristics have been described in the paper. The essential elements are (1) the presence of nests or columns, often partially cystic, of rather uniform size and appearance embedded in (2) a matrix of fibromatous tissue which is sharply marked off from the surrounding ovarian stroma though there is no definite capsule. The tumors probably arise from the so-called Walthard islands of indifferent cells which may at times occur in the ovary, though other explanations have been suggested.

The most interesting histologic characteristic is the frequently observed transition of the cells into a cylindrical type identical with that characterizing the ordinary pseudomucinous cystadenoma, so that large tumors of the latter variety may be produced, with only small nodular Brenner tumor vestiges in the wall to indicate their origin. There is logic, therefore, in the subdivision of Brenner tumors into the solid and cystic varieties. Three such tumors are included in our series. On the other hand the fibromatous reaction may be so striking as to produce large fibromas of the ovary. In such cases, of which 2 are included in our group of cases, the origin is indicated by the finding of the typical cell nests scattered either sparsely or richly throughout the tumor. There is little or no evidence to indicate that Brenner tumors exert any such endocrine effects upon sex characters as those which characterize granulosa cell carcinoma or arrhenoblastoma.

REFERENCES

(1) *Wolfe, S. A., and Kaminester, S.:* Am. J. Obst. & Gynec. **27:** 600, 1934. (2) *Bland, P. B., and Goldstein, L.:* Surg. Gynec. Obst. **61:** 250, 1935. (3) *Te Linde, R. W.:* Am. J. Obst. & Gynec. **20:** 552, 1930. (4) *Orthmann, E. G.:* Monatschr. f. Geburtsh. u. Gynäk. **9:** 771, 1899. (5) *Brenner, F.:* Frankfurtsh. Ztschr. f. Path. **1:** 150, 1908; Inaug. Diss. Würzburg, 1907. (6) *Meyer, R.:* Zentralbl. f. Gynäk. **56:** 770, 1932; Arch. f. Gynäk. **148:** 541, 1932. (7) *Geist, S. H.:* Am. J. Obst. **3:** 231, 1922. (8) *von Szathmáry, Z.:* Arch. f. Gynäk. **154:** 390, 1933. (9) *Varangot, J.:* Gynéc. et obst. **38:** 11, 1938. (10) *Walthard, M.:* Ztschr. f. Geburtsh. u. Gynäk. **49:** 233, 1903. (11) *Plaut, A.:* Arch. f. Gynäk. **153:** 97, 1933. (12) *Akagi, Y.:*

Ibid. **134:** 390, 1928. (13) *Schiller, W.:* Ibid. **157:** 65, 1934; J. Obst. & Gynaec. Brit. Emp. **43:** 1135, 1936. (14) *Fischel, A.:* Ztschr. f. Anat. u. Entwicklsges. **92:** 34, 1930. (15) *Neimann, B. H.:* Arch. Path. **21:** 55, 1936. (16) *Frankl, O.:* Arch. f. Gynäk. **131:** 325, 1937; Zentralbl. f. Gynäk. **58:** 2656, 1934. (17) *Mandelstamm, A.:* Arch. f. Gynäk. **148:** 494, 1932. (18) *Schiffman, J.:* Ibid. **150:** 159, 1932. (19) *Abraham, E. G.:* Ibid. **154:** 565, 1933; Zentralbl. f. Gynäk. **57:** 1113, 1933. (20) *Kleine, H. O.:* Ztschr. f. Geburtsh. u. Gynäk. **114:** 125, 1937. (21) *Freund, R.:* Arch. f. Gynäk. **155:** 67, 1934. (22) *Fauvet, E.:* Ibid. **159:** 585, 1935.

DISCUSSION

DR. WILLIAM C. DANFORTH, EVANSTON, ILL.—I am particularly interested in Novak's explanation of the histogenesis of the Brenner tumor. That the islands of Walthard provide the starting point of these growths seems to be the most widely accepted theory. The essayist suggests the possibility of metaplasia of the germinal epithelium or peritoneum as mechanism for the production of nests of cells which at least resemble the Walthard islands and which may be the point of origin. The explanation of Schiller, that these tumors arise from inclusions in the ovary of epithelium from the embryonic urogenital system, seems less convincing. A third theory, not mentioned by the essayist, that these tumors are to be regarded as a one-sided type of teratoma because of their occasional association with pseudomucinous cystadenomas does not seem to me to be applicable as only a minority of these growths are accompanied by such cystadenomas.

The clinically benign character of these tumors seems quite definitely established and operation need go no further than the excision of the tumor and such other surgery as may seem clearly indicated.

The tremendous variation in size of these tumors was brought out by Novak. In our much smaller series the growths vary from an enormous cystadenoma to a microscopic tumor which was unrecognized on the operating table or in the laboratory on gross examination and was only found on routine section of the ovary.

I will give a brief report of the three cases which have occurred in our own work.

The first was a woman of 45 years, a ward case, already reported by Philip H. Smith. In the right ovary, there was a solid tumor about the size of a hen's egg which proved to be a Brenner tumor of the solid type, containing a number of small epithelial cell nests in some of which are seen the typical vacuoles.

The second case, a woman of 51 years, was a private patient of H. J. Holloway. A large pseudomucinous cyst was found 22 by 10 by 8 cm., containing about 1,000 c.c. of fluid. In the hilum was a solid mass in which were present the usual cell nests characteristic of the Brenner tumor but with a greater amount of mucinous material than the preceding case.

The third case was a patient of my own, a woman of 68 years, who was operated upon for a very early carcinoma of the corpus uteri. Both ovaries appeared entirely normal upon the operating table, and the pathologist noted nothing abnormal about them upon gross examination. Upon routine section small cell nests with the characteristic vacuoles were found. These were much smaller than in the preceding cases, most of the nests not being over 1 mm. in diameter.

DR. LEWIS C. SCHEFFEY, PHILADELPHIA, PA.—I wish to record two interesting and curious cases that have come to our attention on the Gynecologic Ward Service at Jefferson Medical College Hospital. They are interesting because they deal with the development of granulosa cell tumors of the ovary in patients previously treated successfully with radium for carcinoma of the cervix.

CASE 1.—The first patient was a white woman of 54, para x, admitted Oct. 26, 1925. She had developed a bloody vaginal discharge for three months previously, and six years after her menopause. A diagnosis of carcinoma of the cervix, intermediate grade of malignancy (Group III, Schmitz), was made by biopsy and application was made of 150 mg. of radium for twenty-four hours.

Uneventful convalescence followed, with regression of the malignant growth and no apparent recurrence during an observation period of ten years.

The patient was readmitted Sept. 14, 1935, because of a gradual enlargement of the abdomen of four months' duration. Examination showed the cervix to be almost obliterated with moderate contracture of the vaginal vault. The uterus was

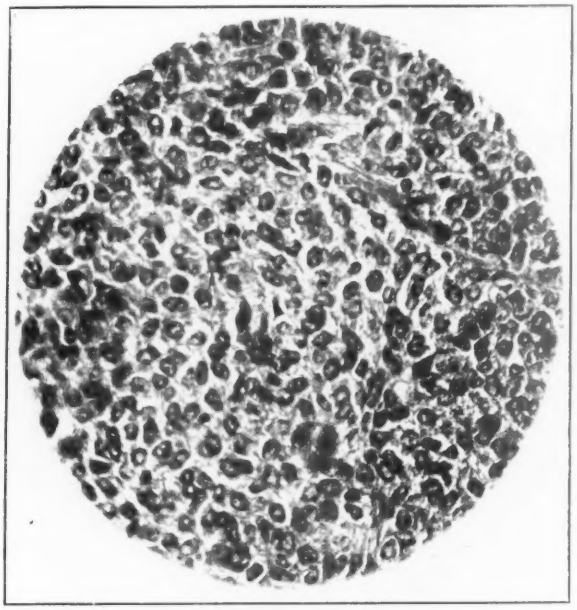

Fig. 1.—Granulosa cell tumor of ovary. High power (×250).

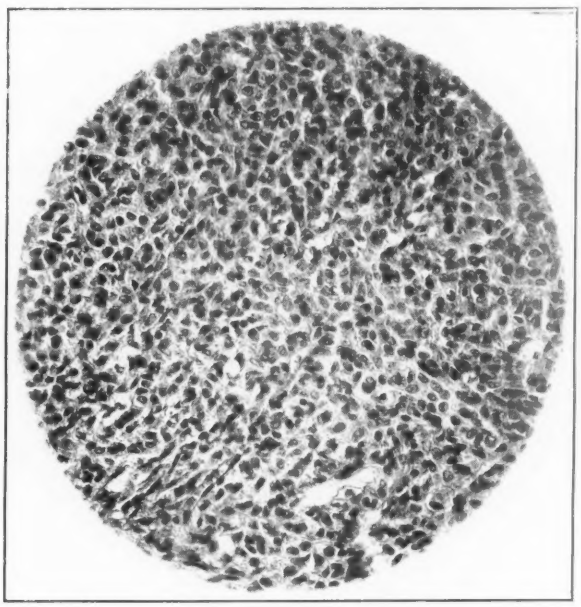

Fig. 2.—Granulosa cell tumor of ovary. High power (×250).

of normal size and position but with lessened mobility. A cystic mas, about the size of a honeydew melon, could be palpated as a freely movable enlargement low in the pelvis. With a preoperative diagnosis of ovarian cyst, I operated upon her on Sept. 19, 1935. Abdominal section revealed a multilocular ovarian tumor, springing from the left adnexal region with a partial twist of the pedicle. The right tube and ovary were normal. The uterine fundus was small, atrophic, and movable. There was no induration of the broad ligaments, and no evidence of carcinomatous areas anywhere in the abdomen. A small amount of brownish fluid was present in the peritoneal cavity. Left salpingo-oophorectomy was performed. The vaginal biopsy showed hyalinized tissue, while the ovarian tumor was described by B. L. Crawford and Hoffman as follows:

Specimen consisted of an oval-shaped cystic and solid tumor which weighed 2,000 gm. and measured 22 by 16 by 14 cm. The cystic portion measured 16 cm. in diameter and was covered by a thin smooth glistening membrane. The solid portion was nodular in shape and measured 10 by 6 by 6 cm. The cyst was unilocular in nature and contained a clear amber-colored serous fluid. The interior of the cyst wall was perfectly smooth. The solid portion on section revealed a friable soft yellowish gray tissue in which many small cystic areas were noted. Some of these cystic areas were filled with a necrotic blood or yellowish gray tissue having the consistency of brain tissue.

The cystic portion was lined by a thin fibrous connective tissue capsule which was partly lined by low cuboidal epithelial cells. The solid portions of the tumor were composed of a very cellular tumor growth. The individual cells resembled the normal granulosa cells of the follicles. In many locations these cells were so grouped as to give the impression of numerous small primordial follicle formations. In some locations these cells presented gyrate formations. A few corpora albicantes were likewise noted (Fig. 1).

Diagnosis: Granulosa cell tumor of the ovary.

This patient has since been seen at regular intervals and has remained well.

Case 2.—R. D. was a white woman, para iv, admitted on Sept. 14, 1930. She had had three previous operations, an appendectomy, 1910; a cholecystostomy, 1911; and a possible supravaginal hysterectomy with unilateral salpingo-oophorectomy, 1912. No written verification of this last operation was obtained, but there had been no menstruation following it during a period of eighteen years. Vaginal bleeding (''spotting'') had occurred intermittently for two years prior to admission at which time a diagnosis of squamous cell carcinoma of the cervix, low grade (Group III, Schmitz) was made. Application was made of 150 mg. of radium for twenty-four hours. Convalescence was uneventful and the patient showed no recurrence of the cervical carcinoma during an observation period of eight years.

The patient was readmitted April 22, 1939, with a history of an enlargement of the lower abdomen of about nine months' duration. Pelvic examination showed an atrophic contracted vaginal vault with some semblance of an external cervical os. Parametrial fixation was present, together with a pelvic mass the size of a four months' pregnancy, which was thought to be an enlarged fundus, probably adherent to a loop of bowel. The preoperative diagnosis was fibroma uteri with intestinal and pelvic adhesions. Abdominal section (May 2, 1939) revealed a cystic tumor, the size of a honeydew melon, which had the appearance of a parovarian cyst, arising from the pelvis. The right uterine tube was attached and spread out over the surface of the tumor, which was semisolid and cystic, being diffusely adherent to the omentum, small intestine and parietal peritoneum. There was no evidence of a uterine fundus or left adnexa. The tumor was mobilized with some difficulty, and the capsule ruptured just before its removal at a point adherent to the rectal wall. The tumor was described by Drs. B. L. Crawford and J. Hoffman as follows: Specimen consisted of a large ovarian tumor which weighed 1,250 gm. and measured 17 by 14 by 11 cm. The tumor was soft and cystic and was covered by a pinkish red capsule which in some areas was duplicated upon itself. A few adhesions were seen on the surface of the tumor. The capsule of the tumor was intact and con-

sisted of ovarian stroma in which corpora albicantes were seen. The tumor proper was composed of many compartments which were composed of granulosalike cells which were arranged in folliclelike formations (Fig. 2).

Diagnosis: Granulosa cell tumor of the ovary.

Convalescence has been uneventful.

DR. GRETA STOHR, NEW YORK, N. Y. (by invitation).—Among 9 cases of tumor ovarii Brenner at the Woman's Hospital, New York, we observed one case which seems to support the theory that these rare tumors might take their origin in the rete ovarii. Similar findings, but none as determinative as the one to be presented, are those described by Schiller and Fauvet. The case represents an accidental finding, since the whole tumor did not exceed a diameter of about 3 mm. It was seated in the hilus of an ovary which was essentially of normal type.

Microscopically we found a peculiar topographical relationship between the rete and the small tumor. The latter, which is a well circumscribed body, composed of the characteristic epithelial nests and the connective tissue stroma, is densely adjacent to the well-developed rete and there is an intimate interweaving of rete ducts and the nests of Brenner epithelium. In detail photographs rete tubules are found in several instances within or on the periphery of Brenner epithelial inclusions. Here seemingly a transition of the simple low cuboidal epithelium into the undifferentiated pavement epithelium has taken place. The production of mucus is apparent in one cystic structure, which is lined partly by Brenner epithelium and partly by the low cuboidal epithelium of the rete tubule. The lumen of the space is filled with a substance, which gives a positive mucicarmin reaction.

Since both types of epithelium take part in the lining of the small cystic space, the exact origin of the mucous matter is not evident. This fact might be better elucidated by the following slide, which reveals a typical tubule of the rete distended by mucous content without the evidence of a morphologic alteration of the epithelium proper. Such structures, therefore, might be considered as indicative of a biologic functional transformation of the tubular epithelium correlated with its morphologic transformation, and as an initial process conducive ultimately to heterotopic tumor formation.

DR. NOVAK (closing).—As I mentioned in my paper, no one can speak with assurance as to the histogenesis of Brenner tumors, and it is quite possible that there is more than one source. For reasons which I have already discussed, the Walthard islands seem to me important, especially since all degrees of transition can be demonstrated between these and the fully formed Brenner tumors.

From a laboratory standpoint one may urge the importance of searching for evidences of Brenner tumor in the walls of cystadenomas and in the structure of fibromas. The microscopic appearance of Brenner tumors is really quite distinctive, so that, once pathologists become familiar with this tumor type, diagnosis will be easy, and the tumor will be found to be not nearly so rare as the present number of reported cases would seem to indicate.

THE EFFECT OF CARCINOMA OF THE CERVIX UTERI AND ITS TREATMENT UPON THE URINARY TRACT*

HOUSTON S. EVERETT, M.D., BALTIMORE, MD.

(From the Department of Gynecology of the Johns Hopkins University and Hospital)

ALTHOUGH the destructive effects upon the urinary tract of untreated and uncontrolled carcinoma of the cervix uteri has been long widely recognized, in recent years a renewed interest has been shown in this subject because of the possible alteration in the course of the disease resulting from its treatment by irradiation. Careful autopsy studies along these lines have been reported by Behney,[1] Faerber,[2] Morton,[3] and Herger and Schreiner.[4] The first three of these articles deal with general considerations as to the alteration of the progress of the disease as a result of irradiation therapy, but the articles of Behney and Morton are of considerable importance because they each record three cases in which death followed very rapidly upon irradiation and could be directly attributed to the treatment. In the three cases recorded by Behney death was due to a massive necrosis and sloughing of the pelvic tissues and in two of these autopsy failed to reveal any remaining carcinoma, thus suggesting the possibility that irradiation therapy may at times cause serious destruction of normal tissues.

The study of autopsy material is always of great value in throwing light upon the course and eventual termination of a disease entity. In the reports mentioned, however, the vast majority of the patients studied had succumbed to the carcinoma. To the clinician and therapeutist it is of far greater importance to know what types of complications may arise as a result of treatment in those patients in whom the highly desired effect of completely eradicating the cancerous process is achieved. Armed with such knowledge the clinician then may attempt to alter the treatment in such a way as to avoid the complications, or finding this impossible, he may add to his therapeutic procedures such measures as may tend to ward off such complications, or alleviate them once they have already arisen. These principles are particularly applicable to complications arising in the urinary tract in patients treated for cervical carcinoma by irradiation.

My interest in this subject was first aroused in 1929, when Dr. Guy L. Hunner and I[5] encountered and reported the case of a patient who, eighteen months after successful treatment for carcinoma of the cervix by radium and deep x-ray, presented herself with a vesicovaginal fistula, dense strictures in the lower ends of both ureters, bilateral infected hydroureter and hydronephrosis, and bilateral pyelonephritis.

*Read, by invitation, at the Sixty-Fourth Annual Meeting of the American Gynecological Society, White Sulphur Springs, W. Va., May 22 to 24, 1939.

The left ureter had perforated spontaneously into the peritoneal cavity, and there were urinary ascites and chronic peritonitis. The patient succumbed and careful autopsy failed to reveal any remaining carcinoma. Again in 1933, I[6] reported 18 cases showing urinary tract complications following pelvic irradiation. Seven of these 18 patients were suffering from vesicovaginal fistula, and 6 of these 7 were proved to have dense strictures of the lower ureters. The other 11 patients all had very dense strictures of both ureters with resulting upper tract damage. Three of these patients had received irradiation for benign lesions, and of the other 15 in whom the treatment had been administered for carcinoma, all but 2, so far as could be determined, were free from carcinoma at the time they presented themselves because of the urologic condition. The absence of urinary tract symptoms previous to irradiation in most of these patients suggested that the conditions found had developed as a result of the therapy, and of course in the cases with fistula no doubt of this fact can be entertained. In our experience, however, it is not unusual to find patients with ureteral strictures and moderate degrees of hydroureter and hydronephrosis who present very few or no localizing symptoms. It is therefore not a wholly justifiable contention that the damage to the upper tracts found in these cases was due entirely to the irradiation. The possibility must be considered that such lesions may have existed previous to irradiation and that they may merely have been increased to the point of producing symptoms by the lapse of time, and especially, as a result of this type of therapy. It was in an attempt to throw further light upon this question that the present study was undertaken.

In planning the study it was hoped that satisfactory answers to the following questions might be found:

1. What types of complications are found in the bladder as a result of irradiation, and with what frequency do they occur?

2. At what stage in its progress does carcinoma begin to encroach upon and occlude the ureters?

3. Does irradiation therapy ever cause a regression and alleviation of such ureteral damage?

4. Does irradiation therapy per se ever result in ureteral damage with stricture formation and upper tract dilatation?

In an attempt to answer these questions 46 patients have been subjected to urologic study before any treatment was administered. Thirty-three patients have been similarly studied from three months to five years after the administration of irradiation therapy. Of these 33 patients, 17 were taken from the group of 46 who had been studied before treatment, while in 16 others such preliminary study had not been carried out. In all of these patients the carcinoma as far as could be determined was either cured or entirely quiescent at the time of study and further follow-up examinations, as recently as time has permitted, show that they have remained so.

The study was begun in 1933 but has been interrupted from time to time due to unavoidable circumstances. During the periods that the work has been in progress, however, the patients have been unselected so far as any influence the presence or absence of urinary symptoms may have exerted. Patients with obviously hopeless Stage IV carcinoma have not been accepted for the preliminary studies, and although a few patients have been studied after treatment in whom there was evidence that the carcinoma had not been arrested, these have not been included in the report, as our primary interest has been in the cured patients.

At the beginning of the study the upper tracts were examined by means of ureteral catheterization and retrograde pyelograms. It was found however that the painful reactions which often followed these procedures made it difficult to induce many of the patients to return for the later examinations. More recently therefore intravenous urography* has been largely used to study the upper tracts, and the more painful procedure of retrograde pyelography has been used in only those cases in which the intravenous method proved unsatisfactory.

With one exception the irradiation therapy has been administered under the direction of Dr. Curtis F. Burnam and his associates at the Howard A. Kelly Hospital, and it is a pleasure to have this opportunity of expressing my thanks for their helpful cooperation.

I. EFFECT UPON THE BLADDER

This phase of the subject has been more thoroughly and adequately studied and reported by others than have the other questions which this report attempts to answer. Aman-Jean[7] in France, and Graves, Kickham, and Nathanson[8] in this country, have stressed the importance of cystoscopic examination of the bladder, before, during, and after treatment as an aid to the evaluation of prognosis, the progress of the disease, and the success or failure of treatment. The latter authors gave the incidence of vesicovaginal fistulas as 62 out of 683 patients studied and of late radiation reaction with ulceration, as 12 out of the same series. It is not made clear, however, how many of these lesions occurred in cured patients, although for the fistulas it is stated that 7 such lesions were found in 226 patients still living.

Dean[9, 10] has made a notable contribution to this subject in reporting and accurately describing late ulcerative lesions occurring in the bladder following irradiation of the uterus. He described three types of reaction to irradiation found in the bladder as follows:

1. Primary erythema occurring within twenty-four hours after treatment and being merely a nonspecific reaction to local irritation.

2. Secondary erythema appearing usually about twenty-eight days after treatment and being a specific reaction to irradiation, probably due to temporary vasodilatation.

3. Tertiary reaction consisting of obliterative endarteritis with sloughing and ulceration of the tissues. These lesions are often covered with grayish slough or gritty deposits and can only be definitely distinguished from carcinomatous invasion by biopsy. They rarely appear earlier than a year and may appear as late as ten years after treatment with an average of two and one-half years.

*The intravenous urography has been done in most instances with 30 c.c. of diodrast very generously furnished by the Winthrop Chemical Company.

A summary of some of the reports of this type of lesion as gathered from the literature is presented in Table I. In view of the relatively small dosage of irradiation that had been given some of these patients, Dean suggested the probability of individual susceptibility of the bladder tissues to such injury. Most of the authors are agreed that unless fistulas develop the ulcers eventually tend to heal, but that the healing process is a slow one. Various types of treatment have been suggested from simple irrigations to fulguration of the ulcer base, but all are agreed that a most important item is the avoidance of further irradiation, a procedure which may well be suggested and carried out unless the lesions are carefully differentiated by biopsy from carcinomatous invasion.

The effects of irradiation upon the bladder as derived from the present study are shown in Tables II, III, and IV. None of the 46 patients studied before treatment showed evidence of carcinomatous invasion of the bladder. In 7 patients, 2 with Stage I carcinoma, and 5 with Stage III of the disease, the bladder mucosa appeared reddened or injected before treatment. In 3 of these, 1 with Stage I, and 2 with Stage III carcinoma, the urine was infected.

TABLE I. SUMMARY OF CASES OF LATE ULCERATIONS OF THE BLADDER GATHERED FROM THE LITERATURE

AUTHOR AND REFERENCE	YEAR	NO. OF CASES	PER CENT OF PATIENTS TREATED	DEVELOPED FISTULAS	TIME BETWEEN TREATMENT AND APPEARANCE OF LESION	TYPE AND DOSAGE OF IRRADIATION
Dean[9]	1927	3		0	14.5-24 mo.	3272 mc. hr.-6694 mc. hr.
Dean[10]	1933	37	About 2.5 7.3 in recurrent cases	Not stated	1-10 yr. Average 2.5 yr.	1.5 to 8 s.e.d. to base of bladder. Average 5 s.e.d.
Newell and Crossen[11]	1935	4	1+	Not stated	2.5-6 yr.	Not stated
Smith[12]	1932	7		2	11 mo. to 6 yr.	2625 mc. hr.-6288 mc. hr. Average 3500 mc. hr. of screened radon
Colby[13]	1933	12	34.3 of cases studied	7	18 mo. to 6 yr.	Most frequent occurrence followed multiple treatment. Four of 9 cases (44%) developed vesicovaginal fistulas.

TABLE II. SUMMARY OF EFFECT UPON THE URINARY BLADDER OF IRRADIATION OF THE CERVIX

ORIGINAL STAGE OF CARCINOMA		I	II	III	TOTAL
Number of cases studied		14	8	11	33
Bladder mucosa reddened with or without edema	No.	2	2	0	4
	Per cent	14.3	25	0	12.1
Bladder mucosa abnormally pale with or without scarring	No.	2	3	2	7
	Per cent	14.3	37.5	18.2	21.2
Ulceration of bladder	No.	1	2	3	6
	Per cent	7.1	25	27.2	18.2
Vesicovaginal fistula	No.	0	1	0	1
	Per cent	0	12.5	0	3

The incidence of late bladder ulcerations in this series, 18 per cent, is considerably higher than in most series previously reported, but this is easily accounted for by the fact that our percentage is calculated on the basis of cured patients actually studied, while most of the other authors have used the total number of patients treated during the period of study as a basis of calculation. As compared with Colby whose percentage is calculated in the same way as ours, our figure is considerably lower.

The reactions described in Table III are perhaps of no great significance as in most instances they were producing no symptoms. They are presented, however, with the thought that they may possibly suggest the way in which the more serious later lesions develop. Cases 149543 and 110917, for instance, at an early study presented

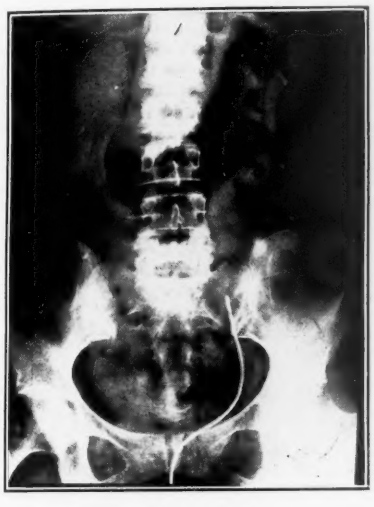

Fig. 1.

Fig. 2.

Fig. 1.—(Case U 43971.) Twelve-minute intravenous pyelogram twenty-six months after 2,100 mc. hr. of radium contracervical and 1,300 mc. hr. intracervical for Stage I carcinoma of the cervix. Note the unusual density of the shadow of the right kidney, but the absence of excretion of the opaque material on this side. The right ureter could not be catheterized due to dense scarring of the right side of the trigone involving the lower ureter, and 40 per cent phenolsulphonephthalein was excreted by the left kidney in a half hour.

Fig. 2.—(Case 149543.) Original Stage II carcinoma complicated by a small uterine fibroid. Left pyeloureterogram made six months after 3,109 mc. hr. of radium emanations and 8,400 r. of deep x-ray therapy. Note moderate dilatation of the ureter and pelvis. Intravenous urograms taken before treatment showed normal tracts, but unfortunately due to marked obesity of the patient the visualization in those plates is not sufficient to permit satisfactory reproductions.

the appearance of erythema, or the secondary reaction of Dean, although in both instances this reaction appeared somewhat later than the twenty-eight days after treatment suggested by that author. Both these patients at later studies showed marked pallor and thickening of the trigone and base, which may be interpreted, it seems, as caused by a mild ischemia resulting from obliterative endarteritis. Such obliterative endarteritis, in severer forms, is generally believed to be the cause of ulceration and fistula formation. Indeed Case 110917 eventually developed multiple ulcerations of the bladder base twenty-two months after treatment. A further confirmation of this idea is afforded by the patient in Case K 83527 who when studied in July, 1937, thirteen months after 3788 mc. hours of radium emanations applied against the cervix and in the canal, showed extreme pallor of the base of the bladder with scattered areas of petechial reddening. This patient returned in March, 1939, thirty-three months after treatment with gross

TABLE III. INDIVIDUAL RECORDS OF PATIENTS SHOWING MINOR BLADDER REACTIONS FOLLOWING IRRADIATION

CASE	AGE	ORIGINAL STAGE OF CARCINOMA	DOSAGE OF IRRADIATION		TIME BETWEEN TREATMENT AND REACTION	REACTION		BLADDER SYMPTOMS	URINE			UPPER TRACT LESIONS
			RADIUM IN MC. HR.	X-RAY IN R. UNITS		DESCRIPTION	TYPE AFTER DEAN[10]		CULTURE	PUS	BLOOD	
U 52299	60	I Stump	2500 i & c*	0	42 mo.	Trigone and base very pale	Mild tertiary	0	0	0	0	0
73250	31	I	1410	0	10 mo.	Trigone reddened	Secondary?	0	0	0	+	0
U 43971	36	I	2100 c 1300 i	0	26 mo.	Pallor and scarring of rt. base and trigone	Mild tertiary	+	0	tr.	tr.	Occlusion of right ureter with functionless kidney. Fig. 1
137399	41	I	1500 c 1600 i	11,760 retreatment after 36 mo.	41 mo. 5 mo.	Localized reddening and edema 4 cm. in diameter rt. base. Healed after two months	Secondary to x-ray	+	*B. coli*	+	0	0
149543	55	II	450 c	8400	3 mo.	Red, edematous trigone	Secondary	+	0	tr.	tr.	Moderate dilatation left ureter. Fig. 2
			2649 i		6 mo.	Trigone and base scarred	Tertiary mild	0	0	0	0	
149764	59	II	2540 i & c	12,180	5 mo.	Base pale with transverse ridges	Mild tertiary	+	0	tr.	tr.	0
U 10901	33	II	2965 i & c	0	6 mo.	Edema and reddening of trigone	Secondary, or cystitis	+++	*B. coli*	+	0	Moderate bilateral dilatation
135255	64	II	Retreatment after 25 mo. 2400 i & c	10,340	34 mo. 9 mo.	Trigone and base pale and rigid	Mild tertiary	0	0	0	0	0

*c, Contracervical; i, intracervical.

110917	57	II	2870 i & c	11,960 re-treatment after 6 mo.	12 mo. after radium	Diffuse reddening entire bladder	Second-ary	+++	0	++	0	Moderate bilateral dilatation. Fig. 3
					20 mo. after radium	Base and trigone very pale with red patches	Mild ter-tiary†	0	0	0	tr.	
K 5814	54	III	1500 i 1500 c 2 gold points in each par-ametrium		60 mo.	Trigone thickened and edematous, granula-tions around right or-ifice	Mild tertiary	++ After x-ray	0	0	0	Moderate bilateral dilatation
			Retreatment after 30 mo. 1600 c		30 mo.							
				8640 re-treatment after 72 mo.	4 mo.							

†This patient developed multiple ulcerations of the base of the bladder twenty-two months after treatment.

TABLE IV. INDIVIDUAL RECORDS OF PATIENTS SHOWING LATE, MORE SERIOUS BLADDER REACTIONS FOLLOWING IRRADIATION

CASE	AGE	ORIGINAL STAGE OF CARCINOMA	DOSAGE OF IRRADIATION		TIME BETWEEN TREATMENT AND LESION	DESCRIPTION OF LESION	BLADDER SYMPTOMS	URINE			UPPER TRACT LESIONS
			RADIUM IN MC. HR.	X-RAY IN R. UNITS				CULTURE	PUS	BLOOD	
100368	28	I	2000 c* 1000 i	0	24 mo.	Necrotic ulceration in rt. base which healed spontaneously	+++	0	+	+	Not determined
K 97218	35	II	2800 i & c	12,420 over 2 mo. Later 13,500 over 2½ mo.	10 mo. from radium. 2½ mo. from x-ray	Trigone pale, scarred on left side	+	0	0	0	Left ureter obstructed
					14 mo. later	Vesicovaginal fistula	+	+	+	0	Functionless left kidney, dilated right pelvis and ureter. Fig. 4
K 80924	50	II Stump	2530 c	0	7 mo.	Small ulcerations in base	+	0	0	+	0
					14 & 17 mo.	Healed, bladder normal	0	0	0	0	
K 83527	57	III	2185 c 1603 i	0	13 mo.	Mucosa very pale with petechial reddening	0	0	0	+	0
					32 mo.	Tertiary ulceration of bladder base	++	0	0	+++	
127093	58	III	2600 c	0	21 mo.	Extensive ulceration of trigone, base, and vesical neck with calcium phosphate encrustations	++++	Mixed	++++	++	Marked bilateral dilatation. Fig. 5
155849	27	III Adenocarcinoma		11,895	8 mo.	Ulcerations and necrosis in base and anterior wall—healed in 3 mo.	+++	0	+	+	0
			2040 i retreatment after 19 mo.	0	2 mo.	Recurrence of ulcer in base	++	0	+	+	0

*c, Contracervical; i, intracervical.

hemorrhage from an extensive ulcerative lesion of the bladder base. A month previous to this last episode she had been entirely free of urinary symptoms. There is absolutely no evidence of remaining carcinoma.

Tables III and IV suggest the role of retreatment in the production of bladder lesions, 4 of the 10 patients with mild reactions, and 2 of the 6 patients with severer lesions having been retreated. None of the 5 patients with bladder ulceration had had more than very moderate dosage of irradiation, suggesting the possibility of individual susceptibility to such a reaction. This is particularly emphasized by Case 155849 who developed extensive bladder ulceration eight months after

Fig. 3.

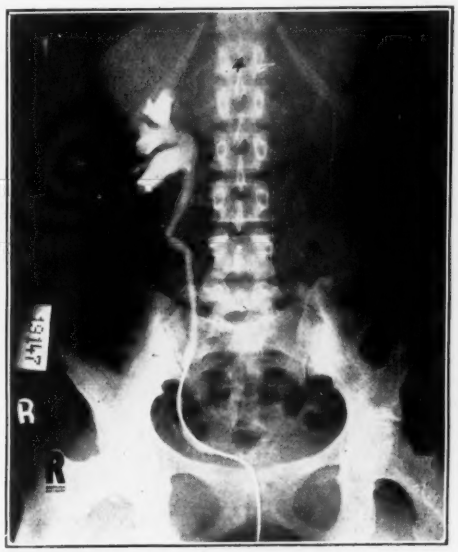

Fig. 4.

Fig. 3.—(Case 110917.) Original Stage II carcinoma. Right and left pyelograms twenty months after original treatment of 2,870 mc. hr. of radium emanations intra- and contracervical, and fourteen months after a retreatment of 11,960 r. of x-ray. At the time of this examination the trigone and base of the bladder showed marked pallor with petechial areas of reddening. Despite the marked bilateral hydronephrosis and hydroureter, the function of these kidneys was unimpaired.

Fig. 4.—(Case 97218.) Right pyeloureterogram twenty-four months after initial treatment of 2,800 mc. hr. of radium emanations for Stage II carcinoma. In addition the patient had been given two courses of deep x-ray therapy, one of 12,420 r. and one of 13,500 r. At the time of this examination she appeared to be well of carcinoma, but had developed a vesicovaginal fistula with complete occlusion of the left ureter and functionless left kidney.

completion of a course of 11,895 r. units of x-ray. This lesion healed but reappeared twenty-one months later, two months after the application of 1,040 mc. hr. of radium emanations. The association of upper tract lesions with the bladder reaction in 7 of these 16 patients suggests that scarring of the bladder wall involving the intravesical portions of the ureters may frequently account for the upper tract damage encountered. The failure to obtain positive bacterial cultures from the urine in most of the cases, even in the presence of blood and pus and actual ulceration, is further evidence that these findings are true reactions on the part of the vesical tissues to the irradiation, and not the result of urinary infection.

II. THE PROGNOSTIC VALUE OF STUDYING THE UPPER URINARY TRACTS BEFORE TREATMENT

Table V shows the results of study of the upper urinary tracts in 46 patients before any treatment was instituted. As was to be expected there is no evidence of any encroachment upon the ureters in patients suffering from Stages I and II

of the disease. In the 28 patients classified by means of vaginal and rectal examination as having Stage III carcinoma, 16, or 57.1 per cent, showed evidence of upper tract damage (Figs. 6, 7, and 8). There has been no evidence of cure or control of the carcinoma in any of these patients, and naturally therefore, no evidence of regression of the ureteral and upper tract lesions. The most interesting group is that comprised by those 12 patients classified by the ordinary clinical methods as having Stage III carcinoma, but who showed no evidence of encroachment upon the ureters. Nine, or 75 per cent, of these patients have survived, and the course of some of them suggests that the induration and fixation felt in the parametrial regions at the time of the original examination may have been due to an associated inflammatory process, rather than to actual extension of the carcinoma. The following case report affords a striking example of this observation.

TABLE V. THE PROGNOSTIC SIGNIFICANCE OF UPPER URINARY TRACT DAMAGE BEFORE TREATMENT

STAGE OF CARCINOMA	NO. OF CASES STUDIED	NO. WITH UPPER TRACT DAMAGE	NO. WITHOUT UPPER TRACT DAMAGE	RESULT OF TREATMENT
I	9	0		
			9	All patients living and apparently well 5 months to 5 years after treatment
II	9	0		
			9	2 died 6 months after treatment. 7 apparently cured
III	28	16		9 died 6 hopeless 1 still under treatment
			12	9 apparently well 1 dead 2 still under treatment

E. M. (Case 118896), white, aged 35 years, was seen first July 28, 1937, complaining of slight vaginal bleeding for seven months. She had undergone a supravaginal hysterectomy in 1924, and had had no bleeding since that time until January, 1937. Examination showed a carcinoma involving the whole of the cervix and extending on to the anterior vaginal wall, with induration in both parametrial regions. The patient had suffered from slight frequency and nocturia but no dysuria. The urinary tract was studied on Aug. 11 and 19, 1937. These studies showed a mild injection of the bladder mucosa and some trabeculation of the base and fundus. There was only an occasional pus cell in the urine, but cultures from the bladder and both kidneys were positive for *Bacillus coli*. The function of both kidneys as determined by the phenolsulphonephthalein excretion was excellent. Retrograde pyeloureterograms of both tracts showed normal findings (Fig. 9). From Aug. 11 to Sept. 10, 1937, the patient received 5,940 R.U. of deep x-ray therapy, and on Aug. 2, 1295 mc. hr. of radium emanations were applied against the cervix and on Sept. 4, 1154 mc. hr. in the cervical canal. The patient appeared to respond poorly. Although the local growth disappeared and the involved areas healed, the induration in the parametria persisted and the patient felt weak and chronically ill.

On Jan. 10, 1938, because of a persistence of bladder symptoms, she was again cystoscoped, but upon this examination the bladder appeared normal and the urine was sterile. In the late Spring of 1938, she began to improve symptomatically

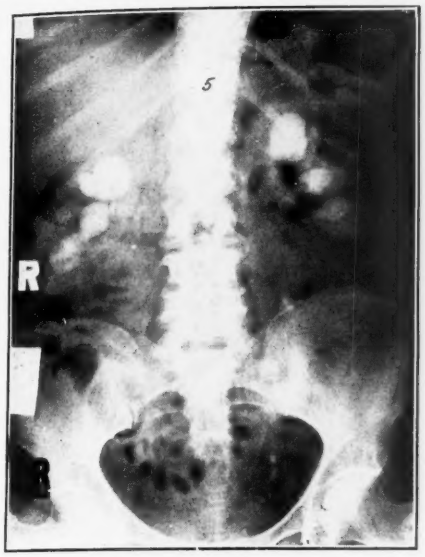

Fig. 5.

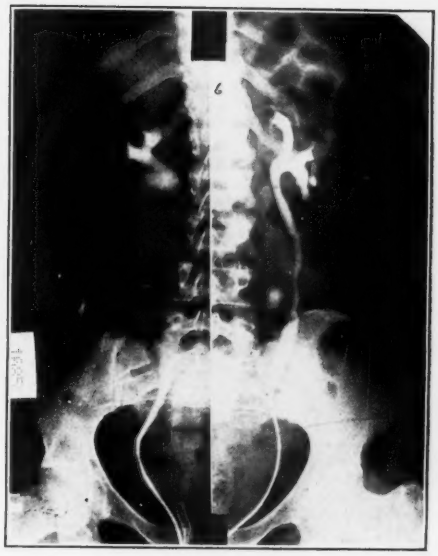

Fig. 6.

Fig. 5.—(Case 127093.) Thirty-three-minute intravenous pyelograms made three years after treatment with 2,600 mc. hr. of radium emanations for supposed Stage III carcinoma. At the time of this examination the patient had been suffering for more than a year from an intense ulcerative cystitis with encrustations, but was apparently well of carcinoma. The films taken earlier than thirty-three minutes showed little visualization.

Fig. 6.—(Case 122344.) Stage III carcinoma. Pyeloureterograms made before treatment. Treatment: 3,500 mc. hr. of radium emanations. Patient died seven months after treatment. Autopsy showed extensive carcinoma with vesicovaginal fistula, destruction of lower end of left ureter, bilateral hydroureter and left hydronephrosis.

Fig. 7.

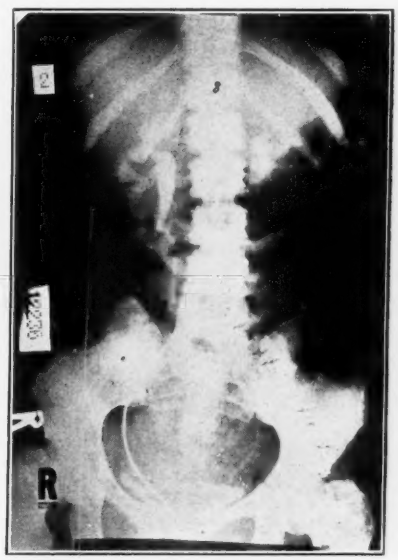

Fig. 8.

Fig. 7.—(Case K 62444.) Stage III carcinoma. Intravenous urograms before treatment. Six months after treatment patient was in the Baltimore City Hospital with a hopelessly advanced carcinoma. Studies there showed a vesicovaginal fistula, a functionless right kidney, and marked dilatation of the left tract. The patient died eight months after treatment.

Fig. 8.—(Case K 41523.) Stage III carcinoma. Intravenous pyeloureterograms with catheter in left ureter, made before treatment. Treatment: 3,000 mc. hr. of radium emanations. The patient died four and one-half months after treatment.

and when she was again studied on July 28, was feeling quite well. Examination at this time, however, showed persistence of induration in the broad ligaments, much scarring of the vaginal vault, and some ulceration at the original site of the tumor. The urine was again sterile and intravenous pyelograms showed rapid excretion and perfectly normal pelves, calyces, and ureters (Fig. 10). Re-examination on Jan. 6, 1939, showed the patient feeling quite well, and that all the pelvic tissues had healed, and the parametrial induration had entirely disappeared.

From the ultimate outcome in this case it would seem that the patient's long chronic illness was probably due to an associated inflammatory process and not to progressing carcinoma, and it seems probable that this should have been suggested by the normal intravenous pyelograms taken on July 28, while massive

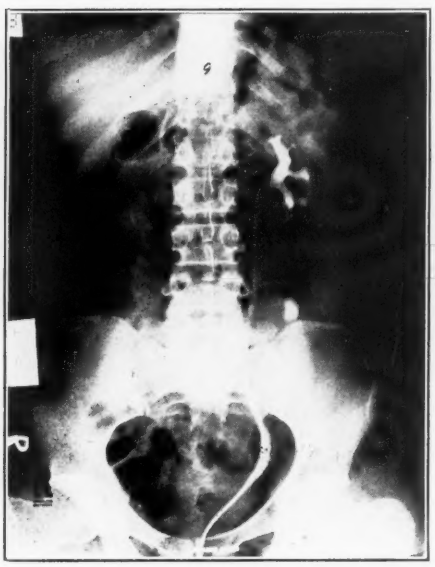

Fig. 9.

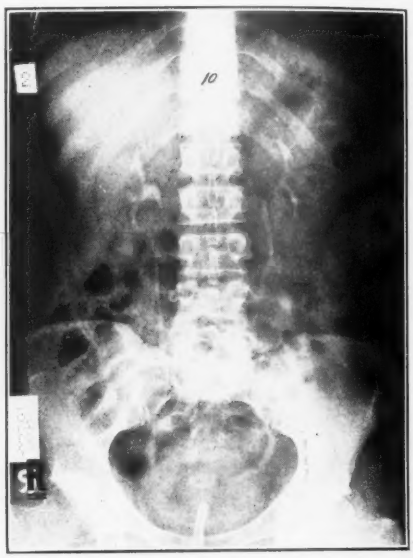

Fig. 10.

Fig. 9.—(Case 118896.) Left pyeloureterogram made before treatment in a patient diagnosed as Stage III carcinoma because of broad ligament induration. Pyeloureterogram of the right side also showed a normal tract.

Fig. 10.—(Case 118896.) Five-minute intravenous urograms taken eleven months after treatment of the same patient illustrated in Fig. 9. The upper urinary tracts appear normal in spite of the fact that there was still parametrial induration. The patient was improved symptomatically, however, and six months later the pelvic induration was no longer present.

pelvic induration still existed. That pelvic inflammatory disease does not tend to produce ureteral obstruction has been suggested by Kretschmer and Kanter,[14] and is further borne out by the patient whose intravenous pyelograms are shown in Fig. 11. At the time these films were made this patient had been suffering for more than two months from a massive postabortal cellulitis. As can be seen from the x-rays there was a mass in the right side of the pelvis sufficiently large to produce marked medial displacement of the right side of the bladder and lower right ureter, but still there is no evidence of dilatation of the upper ureter or pelvis.

III. THE EFFECTS OF IRRADIATION THERAPY UPON THE UPPER URINARY TRACTS

A clear analysis of the clinical literature in regard to this phase of the subject is difficult for two reasons, first because no clear differentiation is made by

Fig. 11.

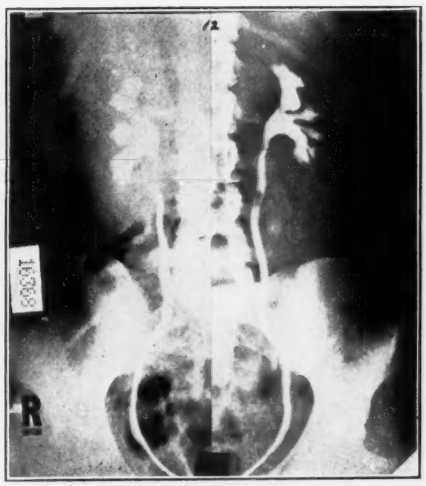

Fig. 12.

Fig. 11.—Intravenous urograms of a patient who had been suffering for two months from a postabortal pelvic cellulitis. Note that there is a right-sided pelvic mass sufficiently large to cause marked displacement of the bladder, but that there is no dilatation of the ureters or kidney pelves.

Fig. 12.—(Case K 96211.) Original Stage I carcinoma. Pyeloureterograms made seven and ten months after 2,700 mc. hr. of radium emanations against the cervix. Patient is still apparently well of carcinoma more than two years since the treatment.

Fig. 13.

Fig. 14.

Fig. 13.—(Case U 10901.) Stage II carcinoma. Bilateral pyeloureterograms six months after 2,965 mc. hr. of radium emanations against the cervix and in the canal. Intravenous pyelograms before treatment showed normal tracts while these show definite but moderate dilatations. The carcinoma was apparently arrested at the time this plate was made.

Fig. 14.—(Case K 5418.) Original Stage III carcinoma. Right pyeloureterogram five and one-half years after first treatment with 4,500 mc. hr. of radium emanations, including gold points in the parametria. Patient had received a retreatment of 1,600 mc. hr. three years after the original treatment and 8,640 r. of x-ray six months before this plate was made. These retreatments were given as precautionary measures and the patient was apparently well at the time of this examination. Note the permanent needle in the right parametrium and note its distance from the ureter.

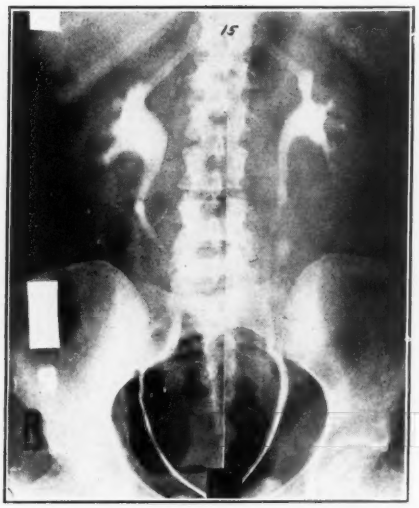

Fig. 15.

Fig. 16.

Fig. 15.—(Case 146745.) Original Stage III carcinoma. Pyeloureterograms made forty-two months after treatment by irradiation. The patient was apparently well of carcinoma at the time of this examination.

Fig. 16.—(Case 155620.) Stage III carcinoma. Fifteen-minute intravenous urogram made before treatment. There was rapid excretion of the dye and rapid emptying of the upper urinary tracts which appear normal.

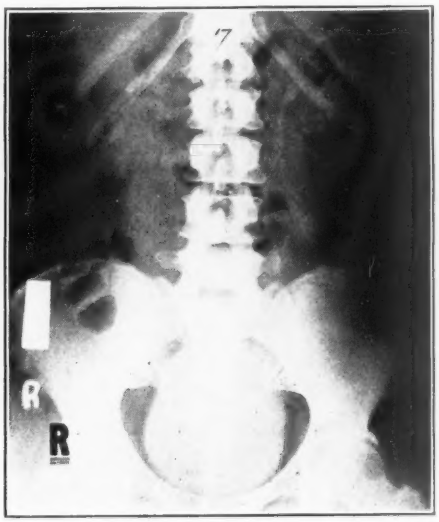

Fig. 17.—Thirty-minute intravenous urogram of the same patient illustrated in Fig. 16, made six months after 3,595 mc. hr. of radium emanations applied against the cervix and 10,340 r. units of x-ray. Pelvic and rectal examination at this time showed the cervix healed and all pelvic tissues soft. The plate shows moderate but definite dilatation of both ureters and much slower emptying than was found in the study made before treatment.

most authors between cured and uncured patients, and second because as yet no reports, so far as I have been able to determine, have been published in which there was a control series studied before treatment. The latter criticism is applicable to the previous report made by the author,[6] and the former to an otherwise very excellent report by Graves, Kickham, and Nathanson.[15] These authors reported 70 per cent of ureteral obstruction in a series of 257 patients studied, but it seems quite clear from their report that in most of their cases the obstruction was due to carcinoma. Bugbee[16, 17] has reported two groups of 8 patients each, in whom he had observed ureteral occlusion and upper tract damage following irradiation of the cervix, but none of the patients in the second group, and only 3 of those in the first seemed to be free of carcinoma. Colby[13] found 35.1 per cent of ureteral obstruction, Herger and Schreiner[4] 50 per cent, and Faerber[2] 56 per cent and 72 per cent of hydronephrosis, but these studies were upon advanced cases, and the urinary tract damage could be directly attributed to the carcinoma. Furthermore in 1926, Martin and Rogers,[18] in an attempt to prove the danger of implanting permanent needles or points directly into the parametria, experimentally demonstrated the dosage of irradiation necessary to produce partial and complete occlusion of the ureter in dogs, when the radium capsule was implanted directly in contact with the ureter. It was found that up to 2.5 skin erythema doses could be so applied without damage, and they claimed that with the ordinary methods of application little more than 1.5 erythema doses of irradiation reached the ureters.

Despite contentions to the contrary, however, such autopsy findings as that reported by Hunner and the author[5] and a strikingly similar case reported by Schmitz,[19] together with cases where the irradiation was administered for benign lesions such as have been reported by Bugbee,[16] Kretschmer,[20] and myself,[6] seem strongly to indicate that irradiation therapy does at times lead to ureteral occlusion and severe damage of the upper urinary tracts.

The results of the study of the present material as regards this phase of the subject are shown in Tables VI, VII, and VIII. The observations on patients originally suffering from Stage III carcinoma, as shown in Table VI, would lead

TABLE VI. SHOWING A COMPARISON OF STUDIES OF THE UPPER URINARY TRACTS BEFORE AND AFTER TREATMENT

STAGE OF CARCINOMA	TIME OF STUDY	NO. OF CASES	IMPASSABLE URETERAL STRICTURE	URETERAL DILATATION	PELVIC DILATATION	FUNCTIONLESS KIDNEY	TOTAL CASES WITH ANY TYPE OF UPPER TRACT LESION
I	Before	9	0	0	0	0	0
	After	14	1 7.1%	3 21.4%	4 28.6%	1 7.1%	5 35.7%
II	Before	9	0	0	0	0	0
	After	8	2 25.0%	4 50.0%	4 50.0%	1 12.5%	5 62.5%
III	Before	28	5 17.8%	12 43.0%	10 35.7%	3 10.7%	16 57.1%
	After	11	0	6 54.5%	3 27.2%	0	6 54.5%
Total	Before	46	5 11.0%	12 26.0%	10 21.7%	3 6.5%	16 34.8%
	After	33	3 9.0%	13 42.4%	11 33.3%	2 6.0%	16 48.4%

to no very definite conclusions, as the percentage of patients showing upper tract damage after treatment is slightly less than was found in the group studied before treatment. If the fact is recalled, however, that none of the patients with this advanced stage of the disease, who showed upper tract damage before treatment, have survived sufficiently long to permit of the later studies, the 50 per cent of upper tract damage, found in 11 patients with apparently cured or arrested carcinoma, is seen to be of considerable significance. The figures in regard to patients originally found to have carcinomas in Stages I or II can hardly be open to question, particularly since the figures in the larger group shown in Table VI are fairly closely approximated by the smaller control group shown in Table VII. It would seem therefore that the figure of approximately 50 per cent showing some degree of upper tract damage after irradiation must be very nearly a true estimate of the incidence of such findings.

A study of Table VIII discloses that in 10 of the patients with evidence of upper tract damage, this damage was very moderate, but in 5 of these 10 the studies were made less than a year following irradiation; while in 4 of the 5 patients showing severe lesions, the studies were made from twenty to forty-two months following treatment. It would seem quite possible therefore, that the moderate lesions observed in the earlier months after treatment, may progress to more serious ones later on. It would seem a wise procedure, therefore, when such moderate lesions are discovered, for the patient to be subjected to a series of ureteral dilatations as prophylaxis against further ureteral contraction and serious damage to the kidneys. Experience with this work, however, has shown that unless patients are suffering considerable pain, which frequently is not the case, they are very reluctant to submit to such prophylactic treatment.

One other point of value is shown in Table VIII, namely that as in the case of the bladder lesions, there is no very striking correlation between the amount of irradiation and the severity of the lesions.

TABLE VII. A COMPARISON OF STUDIES OF THE UPPER URINARY TRACTS BEFORE AND AFTER TREATMENT IN THE SAME SIXTEEN PATIENTS

STAGE OF CARCINOMA	NUMBER OF CASES		IMPASSABLE URETERAL STRICTURE	URETERAL DILATATION	PELVIC DILATATION	FUNCTIONLESS KIDNEY
I	8	Before	0	0	0	0
		After		1 12.5%	2 25.0%	0
II	5	Before	0	0	0	0
		After	1 20.0%	2 40.0%	2 40.0%	0
III	4	Before	0	0	0	0
		After	0	1 25.0%	0	0
Total	17	Before	0	0	0	0
		After	1 5.9%	4 23.5%	4 23.5%	0

CONCLUSIONS

From the above studies the following conclusions seem justified:

1. That the presence of lesions of the upper urinary tracts before treatment in patients with carcinoma of the cervix is of grave prognostic significance.

2. That approximately 50 per cent of apparently cured patients who have been treated for carcinoma of the cervix by irradiation show evidence that the urinary bladder has been affected by the treatment, but that only about 20 per cent show effects that are of any serious significance.

TABLE VIII. INDIVIDUAL RECORDS OF PATIENTS SHOWING UPPER URINARY TRACT LESIONS AFTER IRRADIATION

CASE	AGE	ORIGINAL STAGE OF CARCINOMA	STUDY BEFORE TREATMENT	IRRADIATION		TIME BETWEEN TREATMENT AND STUDY	LESIONS FOUND	CONDITION OF CARCINOMA
				RADIUM IN MG. HR.	X-RAY IN R. UNITS			
U73296	30	I	Neg.	2000 C*	0	9 mo.	Moderate dilatation of rt. ureter and pelvis	Apparent cure
116651	50	I	Neg.	1000 I 2000 C	500	10 mo.	Moderate right hydronephrosis	Apparent cure
K96211	24	I	0	2700 C	0	10 mo.	Moderate bilateral dilatation of ureters and pelves. Fig. 12	Well 2 yr.
U43971	36	I	0	3300 I & C	0	26 mo.	Complete occlusion of rt. ureter; functionless rt. kidney. Fig. 1	Well 44 mo.
137399	41	I	0	3100 I & C	0	30 mo.	Moderate bilateral dilatation of ureters and pelves	Well 46 mo.
149343	55	II	Neg.	3109 I & C	8,400	5 mo.	Moderate dilatation left ureter and pelvis. Fig. 2	Apparently controlled
U10901	33	II	Neg.	2965 I & C	0	6 mo.	Moderate bilateral dilatation of ureters and pelves. Fig. 13	Apparently controlled
135255	64	II	Neg.	2400 C	10,340	46 mo.	Ureter could not be catheterized	Apparent cure
K97218	35	II	0	2800 I & C	25,920	24 mo.	V-V fistula. Left ureter occluded. Left kidney functionless. Hydroureter and hydronephrosis, rt. Fig. 4	Apparent cure
110917	57	II	0	2870 I & C	11,960	20 mo.	Bilateral hydronephrosis and hydroureter. Fig. 3	Apparent cure
150189	58	III	0	3699 I & C	6,000	8 mo.	Marked dilatation right pelvis and ureter. Moderate dilatation left pelvis and ureter	Local cure Bowel met.
127093	58	III	0	2600 C	0	42 mo.	Encrusted cystitis. Slow excretion. Very large hydroureter and hydronephrosis, bil. Fig. 5	Carcinoma well

*I. Intracervical; C. contracervical.

TABLE VIII—CONT'D

CASE	AGE	ORIGINAL STAGE OF CARCINOMA	STUDY BEFORE TREATMENT	IRRADIATION		TIME BETWEEN TREATMENT AND STUDY	LESIONS FOUND	CONDITION OF CARCINOMA
				RADIUM IN MG. HR.	X-RAY IN R. UNITS			
K5418	54	III	0	Gold points in parametria 4500 I and C		5 yr.	Ureters moderately dilated. Fig. 14	Apparently controlled
				1600 I retreatment after 3 yr.	8,640 retreatment after 2 years	2 yr.		
146745	43	III	0	Not known	Not known	42 mo.	Moderate bilateral dilatation of pelves and ureters. Fig. 15	Well
155849	?	III	0	2040 I	11,895	36 mo.	Ureters moderately dilated	Questionable
155620	42	III	Neg. Fig. 16	3595 C	10,340	6 mo.	Ureters moderately dilated. Fig. 17	Apparently arrested

3. That approximately 50 per cent of patients so treated show evidence of some obstructive lesions involving the lower ureters with resulting dilatation of the kidney pelves and the ureters above the point of obstruction, but that again in only about 15 per cent are these lesions sufficiently severe to be of clinical importance.

4. That the incidence of 15 to 20 per cent of serious urinary tract lesions in patients cured of carcinoma of the cervix is sufficiently high to render routine urologic study of such patients a justifiable and important part of the follow-up procedure.

REFERENCES

(1) *Behney, Charles A.:* AM. J. OBST. & GYNEC. **26:** 608, 1933. (2) *Faerber, Hans:* Ztschr. f. Geburtsch. u. Gynäk. **99:** 213, 1931. (3) *Morton, D. G.:* Calif. & West. Med. **42:** 345, 1935. (4) *Herger, Charles C., and Schreiner, Bernard F.:* Surg. Gynec. Obst. **43:** 740, 1926. (5) *Hunner, Guy L., and Everett, H. S.:* J. Urol. **28:** 333, 1932. (6) *Everett, H. S.:* AM. J. OBST. & GYNEC. **28:** 1, 1934. (7) *Aman-Jean, F.:* Bull. de l'Ass. franç. p. l'étude du cancer **22:** 556, 1933. (8) *Graves, R. C., Kickham, C. J. E., and Nathanson, I. I.:* Surg. Gynec. Obst. **63:** 785, 1936. (9) *Dean, Archie L.:* J. A. M. A. **89:** 1121, 1927. (10) *Dean, Archie L.:* J. Urol. **29:** 559, 1933. (11) *Newell, G. M., and Crossen, H. S.:* Surg. Gynec. Obst. **60:** 763, 1935. (12) *Smith, G. G.:* New England J. Med. **207:** 822, 1932. (13) *Colby, F. H.:* Ibid. **209:** 231, 1933. (14) *Kretschmer, H. L., and Kanter, A. E.:* J. A. M. A. **109:** 1097, 1937. (15) *Graves, R. C., Kickham, C. J. E., and Nathanson, I. I.:* J. Urol. **36:** 618, 1936. (16) *Bugbee, H. G.:* Ibid. **32:** 439, 1932. (17) *Idem:* J. Mount Sinai Hosp. **4:** 712, 1938. (18) *Martin, C. L., and Rogers, F. T.:* Am. J. Roentgenol. **16:** 215, 1926. (19) *Schmitz, H.:* Ibid. **24:** 47, 1930. (20) *Kretschmer, H. L.:* J. A. M. A. **89:** 1124, 1927.

THE INFLUENCE OF REPEATED RADIATION ON THE SALVAGE STATISTICS OF CARCINOMA OF THE CERVIX*

LEWIS C. SCHEFFEY, M.D., PHILADELPHIA, PA.

IN THE study of carcinoma of the cervix, there has been a constant endeavor to reach a clearer and more complete estimate of the results of treatment. The term "cure" has been given up since one can never be sure when that point has been reached. We speak of "salvage" as representing the number of years at the end of which the patient is alive and apparently free of the disease. The trend toward a more complete understanding of the effect of cancer therapy was shown a year ago by Kimbrough who pointed out the fact that 20 per cent of the five-year survivals among a series of patients observed at the Hospital of the University of Pennsylvania subsequently died of cancer. Similar findings at Jefferson Medical College Hospital were presented by the author in discussion.

In 1936 Lynch suggested another viewpoint that has impressed us at Jefferson. This dealt with reradiation. He said "Cases are reported as five-year cures, although they have received several courses of roentgen therapy, or have been reradiated during what is intended only for an observation period to determine the efficiency of the chosen therapy." It is of this reradiation and its influence upon salvage statistics that we wish to speak.

We have for a long while followed the plan of Ward, Farrar and Sackett in personally observing cancer patients at appointed intervals after treatment and of reradiating those in whom recurrences were detected. Our statistics deal with comparatively few cases when compared with those of Heyman, Healy and Ward, numbering but 248 from 1921 to 1934. This figure includes all patients with cervical cancer seen in the gynecologic ward service at Jefferson Hospital, and, with few exceptions, treated by Dr. Anspach and myself. During this time our ideas relative to treatment have undergone considerable change for various reasons and in certain details. In the beginning, operative treatment still seemed desirable in some instances and a few patients were subjected to panhysterectomy, but since 1924 we have depended entirely upon radiation. At the outset, and during the period covered by this report, our available radium was in capsules screened with silver and brass (0.3 mm. of silver, 1.0 mm. of brass), and with Monel metal needles (0.3 mm.). We knew very little about filtration. Neither was the deep x-ray therapy the efficient means of radiation that it is at present. For the past few years we have been using high voltage x-ray therapy prior to the application of radium, now screened with platinum (50 mgm. capsules with 1.5

*Read at the Sixty-Fourth Annual Meeting of the American Gynecological Society, White Sulphur Springs, W. Va., May 22 to 24, 1939.

mm. screening, 10 mg. needles with 0.5 mm. screening). The original biopsy is made with the least possible disturbance of the local lesion, and the area from which the specimen is taken is immediately cauterized. For these reasons we believe that the present methods have improved, and that, with better understanding of equipment, appreciation of the need of an accurate measure of filtration and increasing ability to deliver to the depths of the pelvis an adequate dose of the gamma rays, we may hope for better results.

It can be observed that we have been influenced by those pre-eminent figures in cancer therapy, Heyman abroad, Ward, Healy, Lynch, Taussig, Burnam and others in this country. Our statistics have been published from time to time, and what we lack in numbers may, to some extent, be made up by the fact that we have personally examined and kept under repeated observation each of the patients included in this report. Our total follow-up is 97.1 per cent of the patients seen and 98.2 per cent of those treated.

As stated, the phase of the results of radiation that we wish to discuss in this paper is the rôle that repeated radiation for recurrence plays in cancer statistics. A critical review of our patients treated radiologically for cancer of the cervix from this standpoint surprised us with the relative frequency with which prolongation of life has resulted from such a procedure. In our previously published end results, patients who had survived for five years or longer with or without reradiation for recurrence, and alive at the time of the reports, were included as usual in the percentage of absolute and relative cures. In view of the frequency with which patients have been reradiated during the period of salvage, whether it be for five or for ten years, the question has come up with us as to whether it would give a clearer understanding of the situation if it became customary to report: (1) The percentage of all patients living for five years or longer after a single course of therapy, and without evidence of recurrence; and (2) the percentage of all patients living for five years or longer, including those who were treated for recurrence during the observation period. Upon this basis the following data are submitted.

RÉSUMÉ

Two hundred and forty-eight patients with carcinoma of the cervix were admitted for treatment to the Gynecologic Ward at Jefferson Medical College Hospital from 1921 to 1934. Fourteen of these patients were untreated for various reasons, and 7 were treated primarily with surgery. For our immediate purposes, and in order not to confuse the issue with operative treatment, these 21 patients have been excluded from this study which primarily deals with radiated and reradiated patients. (Table I.)

TABLE I. CARCINOMA OF CERVIX, GYNECOLOGICAL WARD SERVICE

Patients admitted	1921-34	248
Untreated	14	
Treated with surgery	7	21
Treated with radiation		227
Follow-up		
Patients seen	97.1 per cent	
Patients treated	98.2 per cent	

TABLE II. RADIATION TREATMENT

	PATIENTS	
Single radium treatment	112	
Multiple radium treatment	22	
Roentgen ray treatment	25	
Radium and roentgen ray treatment	68	227
Subsequent to single radium treatment	43	
Subsequent to multiple radium treatment	18	
Preliminary to radium treatment	3	
Preliminary and subsequent to radium	4	68

TABLE III. RESULTS

39 patients are alive, 5 to 16 years after initial treatment.

Of these, 21 (53.8 per cent) are without evidence of recurrence since the initial treatment, and represent a five-year relative salvage rate of 9.2 per cent.

Inclusion of the remaining 18 patients (46.2 per cent) whose lives have been prolonged by reradiation during the observation period reaches a five-year relative salvage rate of 17.1 per cent.

Two hundred twenty-seven patients were treated with radiation; 134 received radium only, 22 of whom received two or more applications for recurrence at varying intervals; 25 received roentgen ray therapy only; 68 received a combination of radium and x-ray. The roentgen radiation in 43 of these was given subsequent to a single radiation with radium; in 18 it was subsequent to two or more radium applications; 4 received roentgen radiation before as well as after the radium application; 3 received roentgen radiation preliminary to radium. (Table II.)

Of the radiologically treated patients, 39 are alive from 5 to 16 years. Of these, 21 (53.8 per cent) received a single treatment with radium and have survived without evidence of recurrence for the period stated. (Three additional patients died at the respective ages of 70, 67, and 64—10, 12, and 10 years after the single primary treatment, from causes presumably not cancer, but they have not been included in our salvage statistics.) Of the other 18 patients (46.2 per cent), 4 at present show recurrence of the disease 6, 8, 12, and 15 years after the primary treatment and have been reradiated recently, while 14 show no recurrence at present but have received reradiations in the past with radium, x-ray, or both at intervals of from 3 months to 7 years after the primary treatment. (Six additional patients received single radium treatments and lived for 5 to 8 years, and 5 received reradiations with radium and x-ray, and lived for 6 to 10 years, but all died eventually of cancer.) (Table III.)

We find therefore, upon revision, that only 21 patients have had a single course of treatment, and yet never exhibited any evidence of recurrence during an observation period of 5 to 16 years. This group represents at present our relative five-year salvage which stands at 9.2 per cent. If those patients whose prolongation of life has depended upon re-treatment are included, we reach a relative rate of 17.1 per cent.*

SUMMARY AND CONCLUSIONS

1. An incomplete estimate of five-year salvage may result when statistical reports do not take into account the prolongation of life that results from repetition of treatment within the observation period.

2. In our experience, 53.8 per cent of 39 patients alive from 5 to 16 years after initial radiation treatment for carcinoma of the cervix received a single course of therapy. The prolongation of life in the remaining 46.2 per cent has followed reradiation for recurrence during the observation period.

*When all of the 248 patients seen and the 234 patients treated (including those primarily operated upon) are considered, 41 are alive from 5 to 18 years. Twenty-one of these patients have had a single course of therapy and have never exhibited recurrence during the observation period. The five-year salvage of these patients is represented by an absolute rate of 8.4 per cent and a relative rate of 8.9 per cent. The inclusion of patients whose lives have been prolonged by re-treatment represents an absolute salvage rate of 16.5 per cent and a relative rate of 17.5 per cent.

3. The relative five-year salvage rate of patients in the Jefferson clinic, receiving a single course of radiation therapy and remaining free of recurrence thereafter, is 9.2 per cent.

4. The relative five-year salvage rate, including the group of patients whose prolongation of life has been dependent upon reradiation for recurrence, is 17.1 per cent.

REFERENCES

Burnam, C. F.: Radiotherapy, in Curtis' Obstetrics & Gynecology 3: Philadelphia, 1933, W. B. Saunders Co., p. 868. *Healy, W. P., and Frazell, E. L.:* Am. J. Obst. & Gynec. **34:** 593, 1937. *Heyman, J.:* Series of League of Nations Publications, III, Health; 1938, III. 2. *Kimbrough, R. A.:* Am. J. Obst. & Gynec. **36:** 833, 1938. *Lynch, Frank:* West. J. Surg. **46:** 61, 1938. *Scheffey, L. C., and Thudium, W. J.:* Am. J. Obst. & Gynec. **22:** 247, 1931. *Idem:* Ibid. **31:** 946, 1936. *Taussig, F. J.:* Ibid. **36:** 819, 1938. *Ward, G. G.:* Ibid. **22:** 543, 1931. *Ward, G. G., and Farrar, L. K. P.:* Surg. Gynec. Obst. **52:** 556, 1931. *Ward, G. G., and Sackett, N. B.:* J. A. M. A. **110:** 323, 1938.

255 South 17th Street

DISCUSSION ON PAPERS BY DRS. EVERETT AND SCHEFFEY

DR. GEORGE GRAY WARD, New York, N. Y.—What proportion of urinary tract damage is due to irradiation therapy alone and what to the extension of the disease is not easy to determine without the aid of an exploratory laparotomy or autopsy finding. We have abundant proof that ureteral obstruction and resulting kidney damage results from extension of the disease in a large percentage of cases. Notable is Ewing's statement that "the natural termination of most cases of uterine cancer is through uremia from occlusion of the ureters." This has been confirmed by autopsy studies made by many, notably by Wagner, as far back as 1868, by S. Warren, and recently by Behney in his study of 166 cases and by Graves at the Pondville Clinic.

Graves and his co-workers in the Pondville Hospital believe the cause of the ureteral obstruction in most cases is the encroachment of the tumor, but it is also probable that edema following irradiation may precipitate complete obstruction where previous partial obstruction existed due to the disease. Late occlusion may be due to fibrosis from radium or replacement fibrosis following regression of the tumor.

The responsibility of interstitial radiation with needles for ureteral obstruction must be considered. Martin and Rogers' work in 1936 showed that a 1.5 erythema skin dose reaches the ureter with ordinary needle methods and that 2.5 erythema skin dosage can be applied without damage. At the Woman's Hospital it has been our practice to use interstitial radiation with platinum needles in the majority of cases, yet a study of our results does not show a higher percentage of ureteral involvement than most clinics.

Sackett, of our clinic, reported in 1935 complications following radiation therapy in 688 of our cases, and found that the bladder and urethra were involved in 9.8 per cent, and the upper urinary tract in 5.6 per cent. These figures included many transitory symptoms. In 127 cases destined to be five-year cures there were 8.7 per cent bladder and urethra complications, and in 42 ten-year cases there were 4.8 per cent. Patients with upper urinary tract involvement showed in 5.5 per cent five-year survivals, and 4.8 per cent ten-year cures.

I have recently made an analysis of the kidney and ureteral complications in 798 cases of carcinoma of the cervix which we have observed in the Woman's Hospital Clinic from 1919 to 1937.

Of these 798 patients 55 had transitory or permanent kidney or ureteral involvement, or about 7 per cent. These 55 were distributed among the various classes according to Schmitz as follows: Class 1, 3; Class 2, 4; Class 3, 46; Class 4, 2.

Nine of these had or developed fistulas from the carcinoma or radium or both, which implies bladder infection. Of these, 5 were cases of cancer of the cervical stump. One patient was treated by a Wertheim operation with x-rays and two had

no treatment. Three had an associated tuberculosis, one of the kidney, one of the lungs, and one in a cervix with adenocarcinoma.

A careful review of the histories and follow-up notes shows 11 undoubtedly had an involvement of the urinary tract before irradiation. Four were probably due to radium therapy alone, and 41 were probably an extension of the disease.

Ten were perhaps due to radium and the carcinoma combined. No needles were used in 16 cases.

I am in accord with Dr. Everett's statement that the presence of lesions of the upper urinary tracts before treatment is of grave prognostic significance, and his advocacy of a pre-treatment study of the urinary tract, and in the follow-up as indicated, is essential in all cases and is now our custom.

I take it that Scheffey believes we should count as so-called "cured" cases only those who after the initial treatment have no recurrence throughout the five-year period. If a patient requires subsequent reradiation during the five-year period and is free five years after the last reradiation, it seems to me we are warranted in including it in the five-year so-called "cured" cases. I dislike the term "cured" and for a number of years in our reports we use the word "salvaged." Perhaps "arrested" would be a better term as a number of patients die from cancer long after the so-called five-year survival.

DR. WILLIAM P. HEALY, NEW YORK, N. Y.—We have always known that the majority of patients with cancer of the cervix of Groups 3 and 4 die from renal complications. Very few of us have any actual knowledge of the frequency with which these patients are living on a single kidney, and we will not know unless we do routine pyelograms. We must do this investigation as part of our routine preliminary check-up, but it will not change our method of therapy. It will merely give us additional prognostic knowledge. We cannot change our therapeutic method because the cancer which is present is infiltrating not in any one direction but in all directions and must of necessity involve the bladder base and the radiation must extend into the field in which we think the cancer is progressing.

One of our important sources of trouble is definitely that of infection with our radiation. I have just briefly reviewed our last five-year series for 1933. There were 125 primary cases in that year and we had only five vesicovaginal fistulas. All of those patients are dead, and they all died within the five-year period. The fistulas were perhaps somewhat hastened by the use of radium, but they were caused by cancer which continued to grow. It was the disease and not the fistula, of course, that terminated the patient's life.

There were two vesical ulcers in the second and third year following treatment. Both of the ulcers healed under simple therapy. One additional ulcer with cancer of the rectum resulted in death. There were 10 patients in that series five years ago who showed urologic involvement of major importance, and 8 of the patients died within five years of treatment of the carcinoma.

DR. EVERETT (closing).—It is generally acknowledged that the majority of urinary tract lesions encountered in patients with carcinoma of the cervix are due to the carcinoma rather than to the treatment. I believe that in a small percentage of cases there is damage which may, or may not, be due to the treatment, but which is not due to progressing carcinoma as such a condition no longer exists.

I do not want any one to get the idea, as I am afraid was done from my original paper in 1933, that I am criticizing irradiation. I do believe that of the patients who die, a small percentage are lost not because of the carcinoma, but as a result of the urinary tract complications, whether these result from an inflammatory process or a cicatricial scar. I believe that if the patients who seem to be responding to treatment are subjected to routine urologic study, and if upper urinary tract lesions are followed with ureteral dilatations, we may be able to increase the percentage of our salvaged cases.

DR. SCHEFFEY (closing).—I am glad that Ward supported me in regard to the use of the word "cure"; we rather like the term "salvage." The expression "arrested case," as mentioned by Ward, might well be employed in certain instances.

MANAGEMENT OF ACUTE PUERPERAL INVERSION OF THE UTERUS*

S. A. Cosgrove, M.D., F.A.C.S., Jersey City, N. J.
(From the Margaret Hague Maternity Hospital)

ALTHOUGH puerperal inversion of the uterus is said to be one of the rarest obstetric complications, many papers on it have appeared since the turn of the century. Several of the eminent members of this Society have written articles thoroughly competent scientifically and of great literary merit. There are only two reasons why another and less seasoned essayist should attempt further exposition of the subject.

First, it has been well said that no man has seen enough of these cases to know very much, of his own knowledge, about them. Hence, a few more cases detailed and analyzed, with suitable expression of tendencies toward conclusions derivable therefrom, may still have value.

Second, all truth, no matter how thoroughly known to the leaders of medical thought, must be reiterated again and again before it becomes so thoroughly impressed on the rank and file of practitioners as to be available for the benefit of all patients.

Definition.—The usual division of puerperal inversion of the uterus into acute and chronic stages by a time interval of four weeks after onset, is arbitrary and valueless. Kellogg has pointed out the necessity of recognition of a time sequence of pathologic events in the determination of management. This pathologic sequence is typically somewhat as follows:

1. Inversion occurs.
2. Usually after an appreciable, but not generally very long interval, *shock* of greater or less degree supervenes.
   It is during the above described interval that:
   a. Recognition of the inversion is of paramount importance;
   b. Shock treatment may be anticipated or commenced;
   c. Restitution may often be quickly and easily carried out.
   After some further time interval, if there is survival of initial shock,
3. Incarceration by edema and contraction of the cervical ring develops. This may be followed in turn by
4. Strangulation,
5. Necrosis, superficial or massive,
6. Local and systemic infection.

*Read, by invitation, at the Sixty-Fourth Annual Meeting of the American Gynecological Society, White Sulphur Springs, W. Va., May 22 to 24, 1939.

All of these may occur severally or in combination. The time embraced by the whole sequence may vary greatly. Bland states that he has seen massive necrosis supervene in a few hours, while, on the other hand, cases in each of these stages of pathology have presented themselves after intervals of months or years.

It is perfectly obvious that on the occurrence of the accident, we are dealing with a purely mechanical status, of itself relatively simple and innocuous in nature. It quickly, however, becomes urgent, due to hemorrhage and shock. This only is the acute stage of inversion as a pure mechanical entity, capable of treatment concerned only with this mechanism.

As soon as any further pathologic changes whatever occur, one is dealing with a complicated situation comparable to strangulated hernia, appendicitis with rupture, or typhoid perforation. One is now forced to predicate management, as in the other situations cited, on the complications and not the original entity.

At just what arbitrary later time one cares to call chronic, a persistence of any of these complicated pictures, I care not at all. But I do consider it most important to emphasize the above distinction between uncomplicated and complicated inversion.

The general knowledge and beliefs as to puerperal inversion fall into a fairly definite pattern, but on several important points in this pattern there are sharp divergencies of opinion. Instead of reviewing the whole of a subject which has been so often and competently reviewed before, it is proposed to present herewith in brief detail, nine cases of acute puerperal inversion of the uterus not heretofore published. The evidence which they constitute bearing on controversial points will then be assessed and certain conclusions stated.

CASE 1.—A. W. (No. 3178), primigravida, aged 25 years, white; present pregnancy said to have been normal; a private case.

Pains began at 2 A.M. on Feb. 8, 1932, with simultaneous rupture of the membranes. She was admitted to the hospital at 7:30 A.M. the same day. She continued in labor for more than twenty-four hours, at the end of which time there had been twelve hours of full dilatation and active uterine effort without advancement. There was midpelvic arrest in direct occiput posterior. Under ether anesthesia a "modified Scanzoni" was done, a 3,750 gm. baby being delivered at 10:21 A.M., February 9, by a consultant. Nine minutes later the operator suggested that the attending doctor attempt a Credé maneuver. "He gave . . . a shove and the whole uterus came out, with the membranes and placenta attached. I immediately stripped them from the uterus and replaced the latter." There was no shock. The patient's highest temperature was 100° F. on the day of delivery, and she was discharged to the care of her own physician on the tenth post-partum day.

This patient was readmitted at thirty-eight weeks, Aug. 28, 1938, six and a half years after the inversion, in the private care of another physician, and delivered in less than four hours spontaneously, a 3,611 gm. baby, in O.L.A., ran an amorbid post-partum course, and was discharged on the tenth post-partum day.

CASE 2.—E. F. (No. 13239), gravida ii, aged 31 years, white. At nine years of age she had rheumatism, for which she had been bedridden, one year. This was followed by rheumatic heart disease; general history was otherwise negative. She had delivered one child, spontaneous breech, ten years previously.

This pregnancy had been normal except for some dyspnea due to heart disease. At term, first stage began at 3:40 A.M., May 3, 1933; she was admitted at 10:30 A.M.; membranes ruptured at 2:21 P.M. same day. At 3:21 P.M. she delivered a healthy, living girl baby, weighing 3,060 gm. by elective low forceps. Placenta and membranes were expelled completely at 3:32 P.M. the same day. The cord was of the "usual" length and showed no knots or loops. A median episiotomy was performed. Open ether was the anesthetic. She was delivered by an intern. "At approximately thirty minutes after the completion of the third stage the patient's pulse was 140; blood pressure was taken and we were unable to obtain it. The attending doctor was notified. Morphine grain one-quarter was given, 300 c.c. 25 per cent solution glucose was advised; typing and donors were ordered. Patient's color was poor; pulse was rapid and weak. Caffeine (grains 4) was given, and following the infusion of 300 c.c. of 25 per cent glucose, patient was greatly improved. Pulse was 110, fairly strong; blood pressure very low and indefinite. Uterus was relaxed and ballooned up intermittently, and there was a very slow ooze—not an alarming amount. A large clot was expelled. It was decided to pack patient. She was taken to the delivery room, where examination revealed an inverted uterus and bleeding. One thousand cubic centimeters of 10 per cent glucose was started but only a very small amount was given when the patient rapidly became worse and died of air hunger."

Excerpts from autopsy report: ". . . Tubes . . . are markedly congested and drawn into a crater-like cavity over the uterus. The uterus presents a striking picture as the fundus is depressed, and both broad ligaments are drawn into this depression. Only the fimbriated ends of the congested tubes can be seen. Uterus measures approximately 9 cm. in length. The crater . . . 14 by 11 cm. . . . Cervical ring has practically disappeared. Wall of the uterus is very flabby, soft. . . . Uterine fundus is uniformly thin, averages 1 cm. Around the fundus there is a firm ring of the uterine wall measuring 4 cm. in thickness. Microscopic sections show edema and well-preserved muscle cells, otherwise no pathologic changes. . . ."

It is only fair to recognize that chronic rheumatic heart disease, with some symptoms of decompensation, had been recognized clinically in this patient. Autopsy showed extreme deformity of both mitral and aortic valves, and advanced myocardial fibrosis. How much or how little all of this may have contributed to the fatality we do not know. She certainly was not an especially good risk to stand the strain of much hemorrhage and shock.

CASE 3.—M. P. (No. 12656), gravida iii, aged 32 years, white. Obstetric history, first child 6½ pounds, spontaneous delivery. Second child, 9½ pounds—"had trouble." "St. Cecelia Hospital, Humboldt and Richardson Streets, Brooklyn, N. Y., July 11, 1933. . . . Our records show that she had had a severe post-partum hemorrhage which had to be controlled by packing. The delivery was spontaneous in O.L.A."

During this pregnancy she had had headache and spots before the eyes. Pains began at term, 4 A.M., July 5, 1933. She was admitted to the hospital at 7:25 A.M. and delivered spontaneously a 2,800 gm. girl at 2:29 P.M. the same day. During labor a large cystocele, and procidentia were evident, the anterior lip of the cervix appearing in the vulva.

"About ten minutes following the delivery of the child the placenta appeared to be in the vagina. The fundus was massaged and some pressure made from above. No movement of the placenta was noted. Shortly after there was a small rush of blood from the vagina. Thinking that separation had taken place, pressure was again made from above and a 'normal amount' of tension on the cord from below. The placenta was delivered, and in addition there was apparently an acute inversion of the uterus, as the fundus could not be felt abdominally. Following this there was a hemorrhage amounting to about 1,500 c.c. into the membranes and placenta basin; forty minutes after delivery of the child the uterus was replaced manually after the placenta had been manually separated from the uterus. The vagina was packed (4 packs), 1,000 c.c. intravenous glucose given,

transfusion started (750 c.c.) and other usual treatment of shock was given.'' There was prompt good reaction. All packing was removed within twenty-four hours. She ran a low grade morbidity for three days only; was discharged on the eleventh post-partum day and followed in the post-partum gynecologic clinic until Jan. 13, 1934, five months after delivery.

About 16 months ago the patient was operated on in St. Mary's Hospital, Hoboken, N. J. The operation was the repair of the cervix, perineum and cystocele; suspension of uterus. She states that ''she tries not to become pregnant,'' and has not in fact been pregnant since her inversion.

CASE 4.—M. K. (No. 15562), primigravida, aged 21 years, white; normal pregnancy course; at term. Pains began 6 P.M., Feb. 23, 1934; admitted to the hospital at 2:55 A.M., February 23; after 11¾ hours' labor she was delivered by elective forceps in O.L.A. with median episiotomy and second degree extension. The chief resident ''was called to the delivery room because the patient was bleeding more than normal (before delivery) due to a subcutaneous tear of the perineum. Under ether a median episiotomy was done, and a low forceps delivery. Eight minutes after the delivery there was passage of a medium-sized blood clot with some bright hemorrhage, advancement of the cord, and the fundus contracted. One of the interns attempted expression of the placenta, believing that separation had occurred. The fundus relaxed and then completely inverted . . . immediately given 1 c.c. adrenalin and more ether . . . the placenta was completely adherent and attached high on the anterior wall of the corpus. It was rapidly separated and the fundus pushed back. The contraction ring had not yet formed so that the manipulation was without difficulty. There was not 50 c.c. of blood lost during the time of separation of the placenta and the correction of the inversion. . . . I believe the cause of the inversion was slight pressure on a relaxed fundus. There was no traction on the cord nor was the fundal pressure very great. The total blood loss was about 300 c.c. . . . Patient never went into shock. . . .'' There was a mild morbidity for the first four post-partum days and patient was discharged in good condition on the seventeenth post-partum day.

She had a normal spontaneous delivery in O.L.A. of a 4,030 gm. baby after a fourteen hour labor, June 12, 1936, two years and four months after the inversion.

She had a normal spontaneous delivery in O.L.A. of a 3,600 gm. baby after about a two-hour labor Nov. 8, 1937, three years and nine months after the inversion.

CASE 5.—J. C. (No. 19583), gravida ii, aged 34 years, white. Her first baby weighed 7 pounds and was born with instruments at term. On this occasion her pains began 3 A.M., Aug. 21, 1934; admitted 6:45 A.M. the same day; a baby weighing 2,220 gm. was born at 9:17 A.M. the same day, by breech extraction in sacro-L.P. ''Inverted uterus—shock—hemorrhage.'' Amount of blood loss 500 to 600 c.c. ''Patient had a relatively short labor—sacro-L.P. position, breech extraction, under ether anesthesia; following this there was an inversion of the uterus with the placenta and membranes attached. Placenta and membranes were removed; adrenalin given, uterus replaced and packed with 2 to 4 inch gauze packs. Intravenous of 1,000 c.c. of 10 per cent glucose was given. The child was a living girl. The patient's general condition was fair following delivery.'' Another observer notes ''condition on leaving delivery room poor.'' At any rate, at 2:45 P.M. the same day ''the blood pressure was 100/44; the pulse 96, strong; the patient comfortable, fair color. At 5:15 P.M. the blood pressure was 110/75; condition good.'' Temperature was 100.4° F. on the day of delivery; 101.4° F. on the following day. There was no further morbidity. She was discharged on the tenth post-partum day to the care of a private physician. This patient was contacted within the past month and states there have been no further pregnancies as ''she was advised against same.'' Her menstrual periods began three months after delivery and have been entirely regular and normal. She has severe backache at times and feels the womb is slipping down but she avoids medical care because she is fearful that the doctor might recommend an operation.

CASE 6.—H. W. (No. 13023), white, gravida iii, aged 28 years. First child weighed 9¼ pounds, and was delivered after a forty-eight hour labor by forceps.

The second labor was in this clinic. The membranes ruptured at 11 A.M., June 5, 1933, she began to have pains a half hour later; was admitted at 1:05 P.M. the same day; delivery was spontaneous; a 4,620 gm. boy in O.L.A.; there was 400 c.c. post-partum hemorrhage; she was discharged on the ninth post-partum day.

On the present occasion at 12:30 A.M. June 20, 1935, thirty-six weeks pregnant, after an uneventful prenatal course, patient "began to bleed spontaneously, for no discernible cause; no pain. Membranes unruptured. Amount of blood loss, 'at least a pint.' Bleeding has continued since onset. . . ." She was admitted to the hospital at 2:25 A.M. the same day.

The bleeding continued only slightly after admission and the patient was treated expectantly throughout this day, but at 7:30 A.M., June 21, the day after admission, the bleeding having been slight but persistent, the patient was taken to the delivery room. The membranes were artificially ruptured. Blood stained amniotic fluid rushed out. At 7:58 A.M. the patient delivered a cyanotic premature boy with a moderate amount of bleeding, by spontaneous mechanism in O.L.A., under ether anesthesia. It does not appear that the cause of the ante-partum bleeding had been satisfactorily determined. "Conservative methods of expelling the placenta unsuccessful, the placenta being adherent. Credé's method attempted, with the least possible traction on the cord, but the placenta still adherent to the uterus." The resident was advised. The patient continued to bleed moderately and further attempts to expel the placenta were unsuccessful. Uterus became inverted, and the adherent placenta was removed manually, being peeled off gradually at 8:30 A.M. [by the resident]. At 8:35 A.M. the uterus was replaced [by the senior resident] and packed. The patient went into shock and shock treatment was immediately given—adrenalin, caffeine, sodio-benzoate, heat applied, 300 c.c. of glucose given, then 500 c.c. of normal saline. The patient lost a total amount of about 800 c.c. of blood; transfusion of whole blood was given; patient showing improvement after transfusion. Her temperature was at no time above 100.2° F., and this only on two occasions. She was discharged on the tenth post-partum day, July 1; seen once in post-partum clinic July 24. Her premature baby died the day after birth.

This patient has had no further pregnancies. Periods began two months after delivery and have been regular but severely painful. She also complains of a severe pain on the right side which occurs every two or three months but has no relation to her menstruation. She has had no medical care since she left the hospital and says she does not want to have any more babies.

CASE 7.—B. M. (No. 29892), white, gravida v, aged 39 years.

Four previous normal deliveries.

Labor began at 2. A.M., July 9, 1937; admitted to hospital at 6 A.M. the same day. There was a spontaneous delivery in O.R.A. at 12:45 P.M. the same day, under gas-oxygen-ether anesthesia.

"Following spontaneous delivery of baby, attempt was made to deliver placenta ten minutes after birth. At first Credé's maneuver, fetal surface of placenta appeared at vulva; following second Credé without cord traction, the uterus inverted completely." The attending physician was notified. "On inspection the uterus was completely inverted, the placenta attached to fundus, and one-half of it had separated from the anterior wall, the opening of the membranes was around the base of the inverted fundus, the space between being filled with blood. Within twenty minutes after inversion the uterus had been replaced [by an assistant obstetrician present]. He first pushed uterus into the vagina as a piston after the placenta had been removed, then invaginated the left side and finally the fundus entirely, using the other hand abdominally to control. The vagina was packed with two-inch gauze to hold the uterus in place. Patient was in moderate shock. The Trendelenburg posture, morphine sulfate, infusion 1,500 c.c. of 10 per cent glucose and 500 c.c. of citrated blood . . . blood pressure after operation was 114/70, pulse 120 and fair quality." Estimated blood loss 1,300 c.c. Highest temperature was

100° F. on the following day. She was discharged in good condition on the tenth post-partum day. The uterus was small, firm, well involuted, retroverted at a post-partum visit Aug. 25, 1937, but patient "had weakness, dizziness, nausea . . . does not appear . . . in the best of health . . . has puffs under the eyes, anemic."

This patient has not had any subsequent pregnancies. Her periods returned four months after delivery and vary from 18 to 28 days; flow lasting from one to two days. She does not want any more babies. She is pale, thin, nervous, appears to be anemic. She had a thyroidectomy done one year ago.

CASE 8.—A. M. (No. 19299), gravida iii, aged 22 years, white. One previous instrumental delivery after twenty-four hours of labor, of a 7¾ pound baby. One previous spontaneous delivery after a five-hour labor of a 4,480 gm. baby in O.L.A. in our own clinic, Jan. 26, 1935. Present labor began 9:15 P.M., Apr. 14, 1938, at about thirty-eight weeks. She was admitted at 3:15 A.M., Apr. 15, 1938; delivered spontaneously after fourteen hours of labor a 4,060 gm. baby in O.L.A. under gas-oxygen-ether anesthesia, with a second degree laceration of the perineum.

"Placenta showed signs of being free—bleeding—attempt made to express it. This was deferred after no results. Then the laceration was repaired. When repair was finished there was a gush of blood; several attempts made with Credé and cord traction to deliver the placenta. Efforts ceased for ten minutes. With further bleeding, more vigorous attempts at expression made, placenta being in sight. While making manual traction it was discovered that uterine wall was inverted and placenta adherent for one-third of the placental surface. Placenta was peeled off and uterus was replaced manually. Uterine packing and vaginal packing . . . total blood loss 600 c.c. Condition of patient good at this time."

There was no post-partum febrile morbidity and patient was discharged to the care of her own physician on the tenth post-partum day, in good condition. This was barely one year ago, and we have no record of further pregnancy on the part of this patient.

CASE 9.—F. L. (No. 28474), gravida ii, aged 25 years, white. She had had one child Nov. 28, 1936, at term, by spontaneous delivery on the private service in our own clinic.

This pregnancy was uneventful. She delivered spontaneously in O.R.T. after an eleven-hour labor a 2,820 gm. baby at 7:24 P.M., Dec. 22, 1938, under gas-oxygen-ether anesthesia. A right mediolateral episiotomy was repaired, after which "placenta seemed free; delivered by Schultz mechanism with moderate tension on cord and fundal pressure, after the placenta was thought to be in the vagina. Immediately after delivery of placenta the uterus was found low in the pelvis. The fingers were inserted into the vagina to push it up. A globular mass was found and an indentation recognized in the top of the fundus through the abdominal wall . . . with pressure of fingers in the center of the mass in the vagina a dimple formed and the mass gradually was reduced, with obliteration of the fundal cupping. The edges of what was thought to be the portio vaginalis cervicis were seized with forceps, and there appeared to be a laceration in this structure which was bleeding briskly . . . no solution of continuity in the uterine wall above it could be felt. This apparent rent was sutured completely; the suture appeared to adequately control all bleeding. Now, a very much relaxed atonic cervix was demonstrated below the line of suture. It was reefed together by suture on either side. It is believed that the first line of sutures was so placed as to close off the uterus at the internal os. Patient lost 600 to 800 c.c. of blood but did not show a marked degree of shock at any time." However, saline, glucose and 500 c.c. of blood were given intravenously. Patient had a temperature of 101° F. on the third post-partum day; was otherwise afebrile and was discharged on the tenth post-partum day. Uterine drainage appeared unobstructed, involution was satisfactory and rapid, and at six weeks post partum was complete and all injuries healed.

The incidence of acute puerperal inversion of the uterus is one factor concerning which there is perhaps the widest discrepancy.

The unbelievably small figures of Zangemeister and the Dublin Rotunda have been again and again cited. Kellogg has gracefully made fun of them. Irving reports from Boston Lying-in Hospital an incidence of 1:7837 and quotes comparable figures by Maxwell at the University of California Hospital of 1:6500. Davis reports from the Methodist Episcopal Hospital in Brooklyn 1:6500 and Stander from the New York Lying-in Hospital, 1:4000.

During the period covered by the 9 cases presented herewith we have had 39,660 living births. This makes our incidence in this period 1:4,333.

Curiously, our experience has not been consistent. For the period 1913 to 1931, eighteen years, with a service in which more than 20,000 living births occurred, I do not recall or find a record of a single recognized case of acute puerperal inversion. In the last seven years, with a material less than twice as large, we have had 9 cases. I cannot reconcile this difference nor impute it to any particular difference in the handling of the material in the two periods; nor to difference in type of personnel engaged in the work.

The importance of primigravidity in the causation of acute puerperal inversion has been stressed, on the supposed basis that fundal attachment of the placenta is more common in women pregnant for the first time. Data as to the actual implantation of the placenta are incomplete or lacking in most of our cases. However, only 2 of the 9 actually occurred in primigravidas. The other cases ranged in gravidity up to five. In those cases in which the insertion of the placenta was specifically described, the attachment was only partially to the fundal portion of the corpus uteri. The higher incidence in primigravidas is not borne out in this small series.

Another disputed point is the role of mismanagement of the third stage of labor in the production of inversion. The majority of writers unequivocally state that inversion does usually depend on such mismanagement.

Irving on the other hand concludes just as definitely from his careful analysis of much collected material that this factor is of importance in somewhat less than half the cases.

I am quite ready to concede that spontaneous inversion may occur, as it apparently did do in one of our own cases. I agree very definitely with Findley and others, that the uterus must be conditioned, so to speak, by distention and relaxation before it is mechanically possible for this accident to occur. But it would appear from our experience that injudicious management of the third stage is outstandingly important. Six of our 9 cases definitely fall in this category, with 2 other cases open to question, so that possibly 8 out of the 9 were more or less directly caused by such mismanagement.

Advice as to the removal of the attached placenta before attempting replacement of the inverted uterus varies. Of our 9 cases, in 5 the placenta was completely, and in 2 others partly, adherent to the uterus. In each case the placenta was promptly detached as soon as the condition was recognized, and before attempts at reduction.

It appears from this, that danger of increased hemorrhage and shock incident to the removal of the placenta, if recognition is prompt, has been exaggerated. Full advantage should be taken of the increased facility of reduction which the removal of the bulk of the placenta affords.

The place of taxis in the treatment of acute inversion has been accepted very largely as a matter of course by many authors, among them Beck, Bethune, Bland, DeLee, Edgar, Findley, Kellogg, Phaneuf, Schumann and Williams, and several note the simplicity and ease of this maneuver.

D'Errico expresses the matter very graphically, saying that the inexperienced accoucher may waste valuable time "and the golden opportunity to attempt manual replacement at once is lost." Effort should be made to emphasize its early recognition and the technique of manual replacement, which will usually be successful if the condition is recognized early.

Barrows says, however, that "immediate replacement of puerperal uterine inversion is frequently attended with considerable shock and loss of blood and is a dangerous procedure."

Irving makes a strong agrument against immediate reduction, citing much higher mortality records by this course than by others. He proposes laparotomy and reduction by Huntington's method as preferable. He at least implies that immediate manual reduction is not proper. Indeed he goes so far as to say that it is not justifiable except "in a remote farm house in a community where hospital facilities are not available."

Huntington, Irving and Kellogg say: "Manual reposition in some cases is impossible and may be accompanied by such free bleeding that it is questionable if it should be attempted."

There was one death in our series. It has already been detailed. Reinversion was not accomplished or attempted. The patient died in shock due to the tardy recognition of the condition before measures directed to overcoming the shock could be effectively put into operation.

All the other cases were reduced by taxis. There was no special difficulty in the accomplishment of this procedure in any single case. All the patients recovered and all had minimal morbidities.

We have been able to trace all of the 8 surviving patients. Of these the inversion has occurred so recently in two as not to have made subsequent pregnancy possible. One patient has had two spontaneous deliveries since the inversion. Another patient has had one entirely natural and spontaneous delivery. There have been no subsequent pregnancies among the rest.

Two patients only had anything significant in their prior obstetric history. One of them had had 3 prior deliveries, the first with forceps, the other 2 spontaneous, but the third accompanied by sufficiently severe post-partum hemorrhage as to have required transfusion. Another case had had two spontaneous deliveries prior to the one in question, the second accompanied by severe post-partum hemorrhage requiring packing of the uterus.

It is to be regretted that taxis for replacement of the inverted uterus apparently presented so little difficulty that in only two cases has

there been trouble taken to detail the manner in which it was done. Most of the accounts merely state that the inverted uterus was replaced manually, one qualified by saying "without difficulty," one says that the pressure by which the taxis was accomplished was made centrally over the inverted mass; another that the initial pressure was made laterally; in all the rest we are left completely in the dark as to any special mechanism by which the apparently very casual manipulation was accomplished. It is hardly worth while then to enter into any controversy as to the best method of accomplishing taxis. The choice of optimal time for attempting it seems to be very much more important than the particular manner in which it is attempted. I am inclined to agree with Bland, who says that if one method does not promptly succeed, the other may be tried, thus placing this particular problem in the same category of trial and error in which so many obstetric problems appear to properly belong.

Four only out of the 9 patients were transfused. Probably not more than 2 were in such severe shock as to urgently need transfusion.

The cavity of the uterus was packed in only 4 patients, but in 2 others the vagina was packed.

Shock was described as severe in only 3 cases. Its degree was equivocal in 1, definitely present in 2 more, but did not appear in any appreciable degree in 3.

Blood loss would, of course, parallel the shock more or less. There were 4 patients who showed markedly excessive blood loss; 2 others in whom the blood loss was excessive and 3 who definitely did not sustain any unusual degree of bleeding.

Of the 8 survivors, 2 had no febrile morbidity whatever. In 4 others it was minimal and in the other 2 slight. All survivors left the hospital on the regular tenth day of the puerperium, except two who remained eleven and seventeen days, respectively.

The age range was nearly two decades, the youngest 21, the oldest 39. All the patients were white women. General medical history was entirely irrelevant except in one case with history of rheumatic heart disease. All the patients were at term excepting one who was at 36 weeks and another at 38 weeks. The anesthetic was ether in every case, supplementing gas-oxygen in 3 cases.

Who had the skill to replace these uteri so easily by taxis, a procedure averred to be so difficult and dangerous? One was an attending obstetrician; one was an assistant attending obstetrician—this man reduced 3 of the cases, but had been responsible for only one; 2 others were assistant attending obstetricians; the other 3 were residents.

Special procedures: Except the combatting of shock, reduction of the uterus, packing of the uterus or of the vagina, no special procedures were used in this series with two exceptions. Adrenalin was used for its supposed value in relaxing the constricted cervix in 3 cases. There would not appear to be enough difference in the difficulty experienced in the reduction in all of the cases of this series, to indicate that the use of adrenalin did actually contribute to the ease of this manipulation.

In one other case, without having noted Bay Jacobs' suggestion to partly suture the external os after the reduction of acute inversion, the procedure was actually applied successively to the internal os and the external os. No interference with drainage occurred. The uterus involuted rapidly and well. The patient had a minimal morbidity and was discharged on the tenth post-partum day. Six weeks later inspection of the cervix showed perfectly patent cervical canal, with entire symmetry of the os and of the cervix itself.

It is recognized that many hundred cases of inversion of the uterus are more or less perfectly detailed in the literature, and that the present series of 9 cases is inconsiderable in comparison to this large number. It is not inconsiderable, however, as representing experience in a single clinic in a relatively short space of time. The uniformity of characteristics of these cases perhaps has enough significance to permit certain inclinations toward conclusions to be expressed.

CONCLUSIONS

First, the greater number of inversions appear to depend on inexpert management of the third stage of labor. They will therefore occur most frequently in the experience of less experienced obstetricians. In our own series two-thirds of them occurred in the hands of interns.

Second, prompt recognition of the identity of the lesion gives the utmost opportunity for safe management.

Because of these two broad considerations, a most important phase of the management of acute inversion is prophylaxis depending on better management of the third stage of labor.

To this end, better undergraduate emphasis, and better practical supervision in our clinics, must be focused on the best means of handling this phase of labor.

Space will not here permit any considerable discussion of the matter, but, no matter how exhaustive such discussion might be, it could be well summed up in two words, gentleness and patience.

Beyond the vital importance of such prophylactic teaching, educational emphasis should demonstrate: that the condition is not nearly so rare as has been taught; that its potential occurrence should be constantly borne in mind in the presence of suggestive symptoms (unusually prompt, persistent, or profuse bleeding appearing during, or following, the third stage of labor, irregularities in contour or position of the corpus uteri); that early recognition and prompt institution of treatment give best prognosis. Of the 8 cases in our present series in which the condition was promptly recognized and the uterus immediately reposed, all recovered. The circumstances of the death of the other case must be imputed to delay in recognition of the pathology, and institution of treatment.

Given recognition of the condition before the development of severe shock, treatment by taxis would appear to lie well within the capacity of even mediocre obstetricians. I hesitate to advise the average prac-

titioner, working perhaps in forlorn and isolated surroundings, to attempt to handle so serious a complication by taxis without help. Yet I am sure that, were his conditions for delivery even decent, and if he did recognize the condition as soon as it occurred, and did then promptly employ taxis and succeed in reducing the uterus before his patient became markedly shocked (which our experience has proved may readily be the case in the majority of such accidents), then his patient will be better off than if he meets the issue only half way by packing the vagina, transporting her to a more or less remote hospital, and there subjecting her to some operative procedure.

This latter course will probably be that of election in cases in which tentative effort at taxis has not succeeded, or where lack of alertness has permitted deep shock to supervene and become the paramount and determining feature of the clinical picture.

Then, shock having been overcome, Huntington's method may be used.

But in regard to really acute inversion as first defined in this paper, let us teach ourselves and our students to bear always in mind that it can happen; that we must recognize it promptly when it does, that if we do recognize it sufficiently promptly, shock will not be so severe as to prohibit definitive management; that we should immediately institute shock-combating procedures and simultaneously proceed with taxis before complicating conditions have had opportunity to set in.

Acknowledgment is made to Thomas A. Barry, A.B., M.D., and Robert A. Cosgrove, A.B., M.D., for assistance in digesting the references consulted.

REFERENCES

(1) *Barrows, David Nye:* Am. J. Obst. & Gynec. **27:** 105, 1934. (2) *Beck, Alfred C.:* Obstetrical Practice, Baltimore, 1935, Williams & Wilkins Co. (3) *Bethune, W.:* Canad. M. A. J. **29:** 631, 1933. (4) *Bland, P. Brooke:* Practical Obstetrics, Philadelphia, 1932, F. A. Davis Co. (5) *Cooke, Willard R.:* Obstetrics and Gynecology, Curtis, Philadelphia, 1933, W. B. Saunders Co. (6) *Davis, George H.:* Am. J. Obst. & Gynec. **26:** 249, 1933. (7) *DeLee, Joseph B.:* Principles and Practice of Obstetrics, ed. 6, Philadelphia, 1933, W. B. Saunders Co. (8) *D'Errico, Emilio:* New England J. Med. **208:** 1, 1933. (9) *Edgar, J. Clifton:* Edgar's Practice of Obstetrics, ed. 6, Vaux, Philadelphia, 1926, P. Blakiston's Son & Co. (10) *Findley, Palmer:* Am. J. Obst. & Gynec. **18:** 587, 1929. (11) *Huntington, James Lincoln, Irving, Frederick C., and Kellogg, Foster S.:* Am. J. Obst. & Gynec. **5:** 34, 1928. (12) *Irving, Frederick C.:* Obstetrics and Gynecology, Curtis, Philadelphia, 1933, W. B. Saunders Co. (13) *Irving, Frederick C., and Kellogg, Foster S.:* Am. J. Obst. & Gynec. **22:** 440, 1931. (14) *Jacobs, J. Bay:* Am. J. Surg. N. S. **32:** 130, 1936. (15) *Kellogg, Foster S.:* Am. J. Obst. & Gynec. **18:** 815, 1929. (16) *Leff, Morris:* Surg. Gynec. Obst. **68:** 224, 1939. (17) *Phaneuf, Louis E.:* Surg. Gynec. Obst. **48:** 709, 1929. (18) *Rucker, M. P.:* N. E. J. Med. **205:** 22, 1931. (19) *Schumann, Edward A.:* A Textbook of Obstetrics, Philadelphia, 1936, W. B. Saunders Co. (20) *Williams, J. Whitridge:* Williams Obstetrics, Stander, ed 7, New York, 1936, D. Appleton-Century Co.

254 Union Street

DISCUSSION

DR. ALFRED C. BECK, Brooklyn, N. Y.—Although spontaneous inversion does occasionally occur, I believe with Cosgrove that most inversions are due to mismanagement of the third stage of labor. In his series he showed that traction on the cord or pressure on the uterus was responsible for the inversion in possibly 8 of his 9 cases. In 3 of them both of these etiologic factors were operative.

In our clinic where traction on the cord is never allowed and where pressure on the fundus is used only when the uterus is in a state of contraction, there have been no inversions in over 30,000 deliveries. On the other hand, some of my associates who work in hospitals where the supervision is not too good tell me that they are called upon to treat this complication not infrequently. They also state that almost invariably the cause of the inversion is either traction on the cord or pressure on the uterus when the uterus is relaxed.

Cosgrove's recommendation concerning early recognition and prompt reposition is, I believe, very sound. The sooner the uterus is replaced the less should be the shock and the less should be the hemorrhage. If the manipulations are done early, the condition of the uterus should be most favorable for reposition, certainly much more favorable than later on. As a consequence the shock incident to the operation and the hemorrhage should be less. I believe that in the cases in which reposition is not attempted soon after the accident occurs, or in which the shock is very pronounced, it might be better to treat the shock and then employ the simpler abdominal technique recommended by the Boston group.

I have seen three cases which behaved very much like those presented by Cosgrove and were reported to our Analysis Committee in the past two years in Brooklyn. All of these patients, of course, died. They occurred in 77,591 deliveries in Brooklyn, giving us one death from inversion to 25,863 births. The first case was a primigravida who was delivered spontaneously. The placenta was delivered by "gentle traction" on the cord. Five minutes later she went into shock and died within a short time after the inversion had been corrected manually. The second case was also a primipara who was delivered by low forceps. The placenta was expressed by Credé's procedure, which was followed by inversion of the uterus. The vagina was then packed, but she bled through the pack. As a result, the uterus was repositied one-half hour later, but the patient died of shock within one hour. The third patient had a precipitate labor at home at seven months, followed by post-partum hemorrhage. The ambulance surgeon expressed the placenta by Credé's procedure and caused inversion of the uterus. Profound shock followed and the patient died fifteen minutes after admission to the hospital. In all three of these cases, inversion was probably due to mismanagement of the third stage.

DR. RUDOLPH W. HOLMES, CHICAGO, ILL.—I believe it is not debatable that gross mismanagement may be a contributory factor in the production of an inversion, but I am equally convinced that such violent measures may have no effect unless there be some peculiar alterations of the muscular texture of the uterus. Such abnormalities of structure are not necessarily congenital, for repeated inversions are really unique in women during successive pregnancies.

Intestinal intussusception offers a definite parallel to the mechanics of uterine inversion. Both must have some temporary abnormalities of tone of the muscularis to permit their occurrence. Some invagination must supervene before further progress of the depressed area can occur. In the uterus, there are three areas which are peculiarly prone to be the site of an inversion: the placental site, especially if it be near the fundus, and the areas about the two ora fallopii. A depression in the uterine wall occurs and then the "rim of the cup" contracts, forcing the protruding portion more deeply into the uterine cavity. This goes on progressively until the inversion is completed, producing the so-called spontaneous active inversion. There is no question but that spontaneous inversion does occur.

The literature also contains case reports wherein the inverted uterus has spontaneously corrected itself. White, in London, had such a case over a hundred years ago. In one of my own cases, repeated taxis had failed to secure the fundal return. After resting my hands, I again assayed a reduction, but the fundus receded before my fingers, replacement occurring without pressure on my part.

Inversion is, and always has been, an extremely rare obstetric complication. If violent attempts at Credé or the worse Dublin method were material causes of inversion, every other woman in the past century, when these methods were the rule, would have had an inverted uterus. We are doing the profession a grave injustice in maintaining a responsibility upon the attendant when an inversion occurs. Cos-

grove deserves high commendation for his integrity in holding that 8 of 9 cases entirely controlled by his institution were the result of mismanagement, but I believe his enthusiasm for the truth has led him astray. His clinic has had the rare experience of having 9 women with the uterine conditions which made the inversion possible, but errors of management were not responsible.

I believe it is wise to return the uterus at once to its normal position. Then, when contractions permit it, the placenta should be removed. The preliminary removal of the placenta may result in such contraction and retraction that the uterus may not be reposed. Furthermore, the retention of the placenta protects the placental site from infection during the manipulations. Some have advised that the fundus should first be dimpled so that the fundus itself is first returned, and then more lateral areas be pushed up. This means that four layers of uterine muscularis must be passed through the cervical canal. If the ring be tight, this may be an insurmountable difficulty. Most authorities advise that that portion which descended last shall first be reposed, by which process only two uterine layers pass through the cervix at a given moment.

DR. JOSEPH B. DELEE, CHICAGO, ILL.—I would recite briefly nine cases in my own experience:

CASE 1.—After manual removal of the placenta, the uterus turned itself inside out as I was drawing my hand out after revising its interior. I simply pushed it back and packed.

CASE 2.—This woman had a complete inversion which was visible at the vulva. I pushed it back and packed, and when she arrived at the hospital, the uterus had reinverted itself. She recovered.

CASE 3.—This case of inversion had five transfusions and later Spinelli's operation. Five years later I did a cesarean section before term, resected the scar which was paper-thin, and she went home with a live baby.

CASE 4.—In another case, which occurred in the hospital, the inverted uterus followed the placenta. The intern pushed the uterus back, gave ergot and pituitary, and the woman recovered.

CASE 5.—A similar case occurred in my service a few years ago.

CASE 6.—Another patient was dead from complete shock when I arrived at her home.

CASE 7.—The next patient was dead from shock and hemorrhage when my associate arrived.

CASE 8.—Another patient came into my service about the fifth day of the puerperium. As I started to remove a pedunculated fibroid which had appeared at the vulva, the uterus came down through the cervix. I pushed the top of the uterus back and packed. She recovered.

CASE 9.—The last patient came in six weeks after the birth of her baby, with sepsis and inversion. I tried to persuade her to stay in the hospital until I cured the sepsis before operating, but she went to another hospital, where she was operated upon and in a few days died of sepsis.

DR. JOSEPH L. BAER, CHICAGO, ILL.—Cosgrove very properly placed major emphasis on mismanagement as the all-important factor in etiology. Since mismanagement is charged with the responsibility of acute inversion of the uterus, the best treatment here, as elsewhere, is prevention. May I indicate a procedure which in my opinion is vital in correct institutional management of the third stage of labor.

Every well-run institution requires the recording of the minute of birth of the infant and the recording of the instillation of silver nitrate into the infant's eyes. Some require a recording of the time of the delivery of the placenta, but very few pay attention to the time of separation of the placenta.

In our institution we require that the physician in charge of the delivery, whether ward service or private, announce, and the nurse record the minute of separation of the placenta. This necessitates recognition of separation of the placenta. If this is efficiently carried out, it will obviate the too violent efforts at expression of retained or adherent placenta, and this in turn will reduce the likelihood of inversion of the uterus to an unavoidable minimum.

DR. A. COSGROVE (closing).—Beck has indicated that the case histories presented here are an indictment of the type of supervision of the work of interns in our clinic. I feel, however, that if some other clinics had to accept and turn out interns under the same circumstances that we do, they also might share our unfortunate experience. I know that under Beck's very close and meticulous supervision, he will not see inversion of the uterus in his clinic.

Holmes has stressed the importance of other factors than improper handling of the third stage in the causation of inversion. Everyone who has studied the literature or his own cases will agree with what Holmes has stated. One of our own cases very definitely occurred spontaneously.

It seems to me, however, that in presenting a series of cases like this it is important to stress the *remedial* factors. If inversion occurs spontaneously in spite of everything that we can devise to protect the patient, then it is an unavoidable accident. But if it occurs because we have mismanaged the third stage, that is *our* fault, and that is the factor that should be emphasized, because it is correctable. That was my purpose in putting emphasis on that phase of the subject.

The proposal to repose the uterus before the placenta is removed, I shall have to take issue with. Dr. Holmes has earlier in his remarks stressed the importance of beginning the reduction of the uterus at the margin of the constricted ring in order to have the least possible number of layers of uterine muscle simultaneously within the grasp of the ring. It seems to me good sense to extend the logic of his technique to the avoidance of the unnecessary bulk of the placenta within the grasp of the ring. This objective can only be attained by removing the placenta before the uterus is reinverted. In our own experience, we have perhaps been lucky in the results of invariably removing the placenta before reducing the uterus. We have not encountered any instances calling the wisdom of that course into question.

(Additional papers presented at this meeting will appear in the December issue, including those of Drs. T. K. Brown; Matthews and Acken; Calkins; Allen; Schumann; Browne, Henry and Venning. The paper by Dr. L. K. P. Farrar, on "The Condition of the Cervix in 500 Consecutive Cases of Abdominal Hysterectomy" is scheduled for publication in "Surgery, Gynecology and Obstetrics.")

Item

American Board of Obstetrics and Gynecology

The written examination and review of case histories (Part I) for Group B candidates will be held in various cities of the United States and Canada on Saturday, January 6, 1940, at 2:00 P.M. Formal notice of the place of examination will be sent each candidate several weeks in advance of the examination date. No candidate will be admitted to examination whose examination fee has not been paid at the Secretary's Office. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination held in June, 1940.

Candidates for reexamination in Part I (written paper and submission of case histories) must request such reexamination by writing the Secretary's Office not later than November 15, 1939. Candidates who are required to take reexaminations must do so before the expiration of three years from the date of their original examination.

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting in Atlantic City, N. J., on June 8, 9, 10, and 11, 1940, immediately prior to the annual meeting of the American Medical Association in New York City.

Application for admission to Group A, Part II examinations must be on file in the Secretary's Office not later than March 15, 1940.

After January 1, 1942, there will be only one classification of candidates, and all will be required to take the Part I and Part II examinations.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.